DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

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[Docket No. 97N–484P]

Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing new regulations to require manufacturers to follow current good tissue practice, which includes methods used in, and the facilities and controls used for, the manufacture of human cellular and tissue-based products; recordkeeping; and the establishment of a quality program. The agency is also proposing new regulations pertaining to labeling, reporting, inspections, and enforcement that will apply to manufacturers of those human cellular and tissue-based products that the agency is proposing to regulate solely under the authority of the Public Health Service Act (PHS Act) and not as biological drugs or as devices. The agency's actions are intended to improve protection of the public health while permitting significant innovation and keeping regulatory burden to a minimum.

DATES: Submit written comments on the proposed rule by [*insert date 120 days after date of publication in the* **Federal Register**]. Submit written comments on the information collection provisions by [*insert date 30 days after date of publication in the* **Federal Register**].

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit written comments on the information collection provisions to the Office of Information and Regulatory

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Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., Washington, DC 20503, Attn: Wendy Taylor, Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Paula S. McKeever, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, 301–827–6210.

SUPPLEMENTARY INFORMATION:

I. Introduction

FDA is in the process of establishing a comprehensive new system for regulating human cellular and tissue-based products. In an earlier related rulemaking, the agency proposed to define a human cellular or tissue-based product as a ''product containing or consisting of human cells or tissues that is intended for implantation, transplantation, infusion, or transfer into a human recipient * * *'' (''Suitability Determination for Donors of Human Cellular and Tissue-based Products,'' proposed rule (64 FR 52696, September 30, 1999), hereinafter ''donor-suitability proposed rule''). ''Transfer'' is a term used with respect to reproductive cells and tissues, and has also been defined in another related proposal (''Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-based Products,'' proposed rule (63 FR 26744 at 26754, May 14, 1998), hereinafter ''registration proposed rule'').

Examples of human cellular and tissue-based products include cadaveric ligaments, skin, bone, dura mater, heart valves, corneas, blood hematopoietic stem cells, manipulated autologous chondrocytes, and spermatozoa. Certain exclusions from the definition of human cellular and tissue-based products may be applicable and have been discussed in earlier rulemakings (registration proposed rule, 63 FR 26744 at 26748; donor-suitability proposed rule, 64 FR 52696 at 52700).

The regulations now being proposed would require all human cellular and tissue-based products to be manufactured in compliance with current good tissue practice (CGTP). The proposal also contains provisions relating to establishment inspection and enforcement, as well as certain labeling and reporting requirements, which would be applicable to those human cellular and tissue-

based products that the agency is proposing to regulate solely under the authority of section 361 of the PHS Act and not as biological drugs or devices.

The agency also requests consultation from the States on any preemption issues raised by the proposed CGTP rule, specifically with regard to: (1) the need for CGTP requirements to prevent communicable disease transmission through human cellular and tissue-based products; (2) alternatives that would limit the scope of such national requirements or otherwise preserve State prerogatives and authority; and (3) any other issues raised by this proposed rule that could affect State laws and authorities.

A. Background

In February 1997, FDA proposed a new, comprehensive approach to the regulation of human cellular and tissue-based products. The agency announced its regulatory plans in two documents: ''Reinventing the Regulation of Human Tissue'' and ''A Proposed Approach to the Regulation of Cellular and Tissue-based Products'' (hereinafter ''proposed approach document''). FDA requested written comments on its proposed approach and, on March 17, 1997, held a public meeting to solicit information and views from the interested public (62 FR 9721, March 4, 1997).

Since that time, the agency has published two proposed rules that would implement aspects of the proposed approach. On May 14, 1998, the agency proposed regulations that would create a new, unified system for registering establishments that manufacture human cellular and tissue-based products and for listing their products (registration proposed rule at 63 FR 26744). On September 30, 1999, FDA proposed regulations that would require most cell and tissue donors to be tested and screened for relevant communicable diseases (donor-suitability proposed rule at 64 FR 52696 at 52719).

With the present rulemaking, the agency is completing the set of proposals that would implement the new regulatory scheme. In the proposed approach document, the agency stated that it would require that cells and tissues be handled according to procedures designed to prevent contamination and to preserve tissue function and integrity. Thus, the agency is now proposing

to require that establishments that manufacture human cellular or tissue-based products comply with CGTP, which would include, among other things, proper handling, processing, labeling, and recordkeeping procedures. In addition, the proposed regulations would require each establishment to maintain a ''quality program'' to ensure compliance with CGTP.

The proposed CGTP regulations would be contained in title 21 CFR in new part 1271, along with provisions relating to establishment registration and donor suitability that have been proposed previously. Subpart A of part 1271 would set forth scope and purpose as well as definitions. Subpart B of part 1271 would contain registration procedures. Subpart C of part 1271 would set forth provisions for the screening and testing of donors in order to determine their suitability. Subpart D of part 1271 would contain the provisions on CGTP now being proposed. Subpart E of part 1271 would contain certain labeling and reporting requirements and subpart F of part 1271 would contain the inspection and enforcement provisions applicable to those human cellular and tissue-based products regulated solely under the authority of section 361 of the PHS Act. The agency proposes to revoke part 1270 (21 CFR part 1270), which will be superseded by new part 1271.

B. The Tiered, Risk-Based Regulatory Approach

The proposed approach document set out a tiered regulatory scheme, under which human cellular and tissue-based products would be subject to an appropriate level of regulation based on the degree of risk and the necessity for FDA review. Certain human cellular and tissue-based products (e.g., tissues that are more than minimally manipulated) would be regulated as biological drugs or medical devices under the Federal Food, Drug, and Cosmetic Act (the act) and/or section 351 of the PHS Act (42 U.S.C. 262), and thus would be subject to premarket review procedures, among other requirements. FDA is proposing to regulate other human cellular and tissue-based products solely under the authority of section 361 of the PHS Act (42 U.S.C. 264), which authorizes the agency to issue regulations to prevent the introduction, transmission, or spread of communicable diseases. (These products are referred to in this document as ''361 products.'')

The proposed tissue regulations would apply to a wide range of human cells and tissues. To simplify terminology, the proposed regulations refer generally to all human cells and tissues, including reproductive tissue, as ''products,'' and refer to persons who recover, screen, test, process, store, label, package, or distribute human cellular and tissue-based products as ''manufacturers.'' The term ''product'' is a term of art coined under Section 351 of the PHS Act, i.e., ''biological product,'' while the term ''manufacturer'' is used in FDA's current regulations that affect biological products, drugs, and devices. However, Section 361 of the PHS Act, which gives FDA the authority to make and enforce regulations to prevent the spread of communicable disease, does not require use of the term ''product'' to define its scope. The agency has received comments to the first two proposed rules to implement the proposed approach objecting to the use of the terms ''product'' and ''manufacturer'' as applied to human cells and tissues. In finalizing these rules, the agency will consider whether alternative terminology to describe the scope of the regulations should be used.

FDA anticipates that determining the regulatory process for certain cellular and tissue-based products may be complicated. To help answer questions about how a particular cellular or tissue-based product will be regulated, the agency developed the Tissue Reference Group (TRG). The TRG is composed of: (1) Three representatives from the Center for Biologics Evaluation and Research (CBER); (2) three representatives from the Center for Devices and Radiological Health (CDRH); (3) the product jurisdictional officer from each Center; and (4) a liaison from the agency's Office of the Chief Mediator and Ombudsman (OCMO), a nonvoting member. Other FDA staff attend the TRG meetings as needed to discuss issues related to products in their area of expertise. The TRG provides a single reference point and makes recommendations to the center directors regarding product jurisdiction of specific tissue.

In addition, FDA recognizes that further public discussion of how the proposed tissue regulations would be applied to certain categories of human cells and tissues may be warranted due to the complexity or sensitivity of the issues. For example, the agency held a public meeting

to discuss how proposed definitions for ''minimally manipulated'' and ''homologous use''should be applied to human bone allograft products on August 2, 2000. FDA intends to provide further opportunities for public discussion of how the regulatory approach should be applied to reproductive cells and tissue. FDA anticipates that there may be additional needs for discussion through public meetings, public hearings, or guidance as the agency implements the new regulations. The regulatory categories applicable to human cellular and tissue-based products are discussed in greater detail in the registration and donor-suitability proposed rules (63 FR 26744 at 26746; 64 FR 52696 at 52698).

Under the regulatory scheme being proposed at part 1271, all human cellular and tissue-based products, regardless of the regulatory category in which they belong, would be subject to certain core requirements designed to address concerns common to all such products. (These core requirements will cover registration procedures, donor testing and screening, and CGTP, and will be in subparts B, C, and D of part 1271.) Because of their nature as derivatives of the human body, all human cellular and tissue-based products pose a potential risk of transmitting communicable diseases. Thus, the donor-suitability proposed rule would require that most cell and tissue donors be tested and screened for evidence of relevant communicable-disease infection. Similarly, the CGTP regulations now being proposed are designed to prevent the introduction, transmission, and spread of communicable diseases. For example, compliance with CGTP would require such precautions as cleaning of facilities and equipment, storage procedures designed to prevent product mix-ups, and controls over processing to prevent product contamination and impairment to function or integrity.

Those human cellular or tissue-based products regulated solely under the authority of section 361 of the PHS Act would be subject only to the requirements contained in part 1271. In contrast, human cellular or tissue-based products regulated as devices or biological drugs would be subject not only to the core requirements contained in subparts B, C, and D of part 1271, but also to other applicable statutory and regulatory requirements.

C. Legal Authority

FDA is proposing to issue these new regulations under the authority of section 361 of the PHS Act. Under section 361 of the PHS Act, FDA may make and enforce regulations necessary to prevent the introduction, transmission, or spread of communicable diseases between the States or from foreign countries into the States. (See sec. 1, Reorg. Plan No. 3 of 1966 at 42 U.S.C. 202 for delegation of section 361of the PHS Act authority from the Surgeon General to the Secretary, Health and Human Services; see 21 CFR 5.10(a)(4) for delegation from the Secretary to FDA.) Intrastate transactions may also be regulated under section 361 of the PHS Act. (See *Louisiana* v. *Mathews*, 427 F. Supp. 174, 176 (E.D. La. 1977).)

Certain diseases, such as those caused by the human immunodeficiency virus (HIV) and the hepatitis B and C viruses, may be transmitted through the implantation, transplantation, infusion, or transfer of human cellular or tissue-based products derived from infected donors. The agency has, in an earlier rulemaking, proposed that most cell and tissue donors be screened and tested for these and other relevant communicable diseases (donor-suitability proposed rule, 64 FR 52696 at 52720). However, donor screening and testing, although crucial, are not sufficient to prevent the transmission of disease by human cellular and tissue-based products. Rather, each step in the manufacturing process needs to be controlled. Errors in labeling, mix-ups of testing records, failure to adequately clean work areas, and faulty packaging are all examples of improper practices that could lead to a product capable of transmitting disease to its recipient. Similarly, as noted in the proposed approach document, improper handling of a human cellular or tissue-based product can lead to bacterial contamination of the product or to cross-contamination between products.

In addition to the direct transmission of communicable disease agents by human cellular and tissue-based products to their recipients, the agency is also concerned about the spread of communicable disease through the use of products whose function or integrity have been impaired. When a product does not work in a patient because it has not been manufactured properly, the risk of introducing, transmitting, or spreading a communicable disease is increased each time a

procedure is repeated for at least two reasons: (1) Despite the best controls, there is a risk, albeit smaller than without controls, of communicable disease transmission, and (2) a procedure for transfer or transplant can carry an independent risk of communicable disease transmission. For example, use of a product whose function or integrity may have been compromised could create a circumstance that increases a patient's need for an additional transfer or transplant attempt. A repeat surgical procedure necessitated by the damaged product would further expose the patient to the additional communicable disease risks inherent in any such procedure. Moreover, a patient in a weakened state from the first unsuccessful procedure is at greater risk of contracting a communicable disease by experiencing a repeat procedure. Therefore, the agency considers that requirements aimed at maintaining product function and integrity are necessary, and thus may be issued under section 361 of the PHS Act.

The proposed CGTP regulations would govern the methods used in, and the facilities and controls used for, the manufacture of human cellular and tissue-based products. CGTP requirements are a fundamental component of FDA's risk-based approach to regulating human cellular and tissue-based products. Products that the agency is proposing to regulate solely under section 361 of the PHS Act and proposed part 1271, would be subject to less rigorous agency oversight than products also regulated under the act and/or section 351 of the PHS Act. By requiring that 361 products be manufactured in compliance with CGTP, in combination with the other proposed requirements in part 1271, the agency can be assured that 361 products are subject to sufficient regulatory controls to protect the public health.

FDA is proposing that the CGTP regulations would supplement, but not supersede, the current good manufacturing practice (CGMP) and quality system (QS) regulations applicable to drugs and devices in parts 210, 211, and 820 (21 CFR parts 210, 211, and 820). Under the proposed rule, human cellular and tissue-based products regulated as biological drugs under the act and section 351 of the PHS Act, or as devices under the act, would have to be manufactured in accordance with CGTP, in addition to existing requirements. Thus, in keeping with the plan outlined in the

proposed approach document, those products regulated as biological drugs or devices would be subject to more comprehensive regulation of manufacturing than the 361 products.

In the donor-suitability proposed rule, the agency proposed to amend the existing CGMP regulations for drugs and the QS requirements for devices to incorporate the testing and screening provisions of proposed part 1271, subpart C. At that time, in order to obviate the need for further revisions, the agency also proposed to amend those sections to incorporate the current good tissue practice procedures of proposed part 1271 subpart D. In amending the CGMP and QS regulations, FDA is relying both on the authority provided by section 361 of the PHS Act to make regulations to prevent the spread of communicable disease, and on its authority under the act to issue CGMP regulations (section 301(a)(2)(B) and (h) of the act) (21 U.S.C. 351(a)(2)(B) and (h)), section 520(f)(1) of the act (360j(f)(1)); section 701 of the act (21 U.S.C. 371)).

Under proposed 21 CFR 210.1(c), the manufacturer of a human cellular or tissue-based product regulated as a drug or biological drug would be required to comply with the CGTP procedures in part 1271, subpart D (donor suitability proposed rule, (64 FR 52696 at 52699 and 52719)). Likewise, under proposed 21 CFR 820.1, the manufacturer of a human cellular or tissue-based product regulated as a device would be required to comply with the same procedures (donor suitability proposed rule (64 FR 52696 at 52699 and 52719)). If the manufacturer failed to follow the CGMP requirements, including the good tissue practice procedures in part 1271, the product would be adulterated under section 501(a)(2)(B) of the act.

FDA is also relying on its authority under section 361 of the PHS Act to propose several reporting, labeling, inspection, and enforcement provisions. Because products regulated under the act and/or section 351 of the PHS Act, are subject to similar regulation requirements, these provisions would apply only to 361 products. Proposed subpart E of part 1271 contains regulations on reporting and labeling pertaining to 361 products and is discussed in section III of this document. Proposed subpart F of part 1271 contains inspection and enforcement provisions also applicable only to 361 products; the relevant discussion appears in section IV of this document.

II. Summary of the Proposed CGTP Regulations

The regulations being proposed would require manufacturers of human cellular and tissue-based products to follow CGTP, which includes proper handling, processing, storage, and labeling of human cellular and tissue-based products, recordkeeping, and the establishment of a quality program. The proposed CGTP regulations are designed to address issues common to all human cellular and tissue-based products, and so are intentionally broad in scope. The agency anticipates that, as it implements the new regulations, there may be additional need for discussion, through public meetings, public hearings, or guidance, of how these general regulations would apply to specific types of products. In addition, there may be specific elements of these proposed requirements that some readers may not consider appropriate to general application. The agency welcomes comments that will assist it in achieving the proper balance between generality and specificity in these regulations.

A. General Provisions (Proposed §§ 1271.150 and 1271.155)

Proposed § 1271.150 contains general provisions intended to aid in the interpretation of the requirements contained in subparts C and D of part 1271. Proposed § 1271.155 sets out the procedures for obtaining an exemption or variance from one or more of these requirements.

1. Current Good Tissue Practice (Proposed § 1271.150(a))

Proposed § 1271.150(a) states that CGTP requirements govern the methods used in, and the facilities and controls used for, the manufacture of human cellular and tissue-based products. CGTP requirements are intended to prevent the introduction, transmission, and spread of communicable disease through the use of human cellular and tissue-based products by helping to ensure that: (1) The products do not contain relevant communicable disease agents; (2) they are not contaminated during the manufacturing process; and (3) the function and integrity of the products are not impaired through improper manufacturing, all of which could lead to circumstances that increase the risk of communicable disease transmission. ''Manufacture'' as defined in the registration proposed rule, includes, but is not limited to, any or all steps in the recovery, processing,

storage, labeling, packaging, or distribution of any human cellular or tissue-based product, and the screening and testing of a cell or tissue donor (proposed § 1271.3(f), 63 FR 26744 at 26754.) The definition of ''human cellular or tissue-based product'' as revised in the donor suitability proposed rule, is intended to cover such products at all stages of their manufacture, from recovery through distribution (see proposed § 1271.3(e) (64 FR 52696 at 52719). For a human cellular or tissue-based product to be manufactured properly, CGTP must be followed in each step of the manufacturing process.

The word ''current'' is included in the term ''current good tissue practice'' because the agency recognizes that appropriate practices may change over time, as research is conducted and new manufacturing methods are developed. These regulations are not intended to require that practices considered current at the time of issuance of the final regulations be maintained indefinitely; instead, the obligation on an establishment is to maintain up-to-date practices over time. Recognizing that improved manufacturing techniques may be developed, the agency has generally refrained in these proposed regulations from requiring specific procedures, such as particular processing methods or storage temperatures. Instead, the proposed regulations set out general objectives. This approach not only allows for new developments, but also affords establishments flexibility in developing procedures that are both appropriate to their particular operations and that comply with the regulations.

The proposed requirements are based on current good industry practice and are intended to address what the agency considers important minimum criteria for the manufacture of these products. In developing these regulations, the agency has reviewed several sets of industry standards, including those issued by the American Association of Tissue Banks (AATB) and by the Eye Bank Association of America (EBAA). The agency expects that some establishments will need to make only small changes in their operations to achieve compliance. Other establishments may find that complying with the new requirements entails revising certain procedures and recordkeeping practices, but few operational changes. Another group of establishments--for

example, those that have not previously been subject to regulation and that do not belong to any standard-setting or accrediting organization--may need to revise their procedures more completely, in order to bring them into compliance with these regulations and industry practice.

Proposed § 1271.150(a) states that CGTP requirements are set forth in subparts C and D of part 1271. The CGTP provisions specifically governing donor suitability, including donor testing and screening, are set out separately in subpart C of part 1271. The agency notes that § 1271.90 contains exceptions from required testing and screening for two types of human cellular and tissue-based product: Banked cells and tissues for autologous use, and reproductive cells or tissue donated by a sexually-intimate partner of the recipient for reproductive use (64 FR 52696 at 52723). (Donor testing and screening are recommended, however.) The agency specifically notes that the exceptions in § 1271.90 apply only to subpart C of part 1271 and do not extend to the provisions of subpart D of part 1271. Because the safety concerns addressed by the proposed CGTP requirements apply to all human cellular and tissue-based products, no exceptions are being proposed for any particular category of product. Thus, banked cells and tissues for autologous use, and reproductive cells or tissue donated by a sexually-intimate partner of the recipient for reproductive use, would be subject to the CGTP requirements in subpart D of part 1271.

2. Compliance With Applicable Requirements (Proposed § 1271.150(b))

FDA recognizes that several establishments may be involved in the manufacture of a single human cellular or tissue-based product. For example, one establishment may recover tissue from a cadaver, another establishment may make the donor-suitability determination, a third may process the tissue, and a fourth may distribute the product. The agency has taken care, in designing these proposed regulations, to reflect the fact that manufacturing roles might be divided up in a variety of possible ways. Thus, under proposed § 1271.150(b), an establishment that engages in only some operations subject to the regulations in subparts C and D of part 1271 need only comply with those requirements applicable to the operations in which it engages. Under § 1271.150(b), an establishment that does not process cells or tissue would not be obligated to establish and maintain

process controls under proposed § 1271.220. However, an establishment that engages another establishment, under a contract, agreement, or other arrangement, to perform any step in the manufacturing process, would be responsible for ensuring that the work is performed in compliance with the requirements in subparts C and D of part 1271. One method of accomplishing this might be by performing periodic audits.

Given that the steps in manufacturing a single human cellular or tissue-based product may be carried out by several establishments, FDA considers it essential that additional safeguards be established to ensure compliance with regulatory requirements throughout the manufacturing process. The agency has considered various ways of allocating regulatory responsibilities among the establishments involved in manufacturing a human cellular or tissue-based product. The agency seeks to permit establishments to maintain flexibility in sharing manufacturing responsibilities, while ensuring that products made available for release maintain their function and integrity, are not contaminated, and do not contain communicable disease agents.

The agency first considered assigning overall responsibility for ensuring that a human cellular and tissue-based product is manufactured in compliance with all applicable regulations to the establishment that determines donor suitability. However, the agency recognized that the role this establishment plays in the manufacture of a human cellular or tissue-based product occurs early in the sequence of manufacturing events. As a practical matter, the establishment that determines donor suitability might not be able to ensure that later manufacturing steps, such as processing and labeling, are performed in compliance with the regulations. A more pragmatic approach would be to assign responsibility to the establishment that makes a product available for distribution.

Another option would be to permit the establishments engaged in the manufacturing process to decide among themselves which party bears ultimate responsibility for the product. However, the agency is concerned that, under this approach, there would be occasions when no establishment would step forward as the one ultimately responsible, and that as a consequence compliance with certain requirements might not be accomplished. As a result, products might be released that pose

a risk of transmitting communicable disease or otherwise increasing the risk of disease transmission. For the same reasons, FDA has rejected the idea that designating a responsible establishment is unnecessary.

The agency has also considered a ''cascading'' set of responsibilities. Under this approach, an establishment would be responsible for ensuring that its own operations comply with applicable requirements, and also would bear the burden of proof that operations performed by other establishments prior to its receipt of the cells or tissue were performed in compliance with applicable requirements.

After considering the unique nature of the cell and tissue industry, and each of the above options, the agency has tentatively concluded that the best approach is to assign ultimate responsibility for the product to the establishment that is responsible for making the product available for distribution. This is consistent with the proposed approach document, which stated that ''[t]he establishment or person responsible for determining suitability of release of cells or tissues would be responsible for ensuring that required screening and testing had been performed prior to final release of the material.'' Thus, proposed § 1271.150(b) states that the establishment that determines that a product meets release criteria and makes the product available for distribution, whether or not that establishment is the actual distributor, is responsible for ensuring that the product has been manufactured in compliance with the requirements of subpart C and D of part 1271 and any other applicable requirements.

The agency specifically requests comments on the allocation of overall manufacturing responsibility. Examples of industry arrangements currently in existence would be particularly useful to the agency in evaluating the comments on these proposed regulations.

3. Compliance With Parts 210, 211, and 820

The proposed CGTP regulations are similar to the CGMP requirements applicable to drugs and the QS requirements for devices. However, the CGMP and QS regulations do not contain provisions specifically intended to prevent the spread of communicable disease. In contrast, the

purpose of the proposed CGTP regulations is limited to preventing circumstances that increase the risk of introduction, transmission, and spread of communicable disease; the proposed regulations are therefore less extensive in scope than the CGMP and QS regulations.

Proposed § 1271.150(c) states that, with respect to human cellular and tissue-based products regulated as biological drugs or as devices, the proposed CGTP procedures will supplement, not supersede, the CGMP and QS requirements. Proposed § 1271.150(c) states that, in the event that it is impossible to comply with all applicable regulations, the regulations specifically applicable to the biological drug or device in question shall supersede the more general.

4. ''Where Appropriate''

Several of the requirements contained in part 1271, subpart D, are qualified by the term ''where appropriate,'' which as explained in proposed § 1271.150(d), are considered to be appropriate, and must be followed, unless an establishment can justify otherwise, and maintains documentation of that justification. Under proposed § 1271.150(d), a requirement is ''appropriate'' if nonimplementation could reasonably be expected to result in the: (1) Product's not meeting its specified requirements related to preventing the introduction, transmission, and spread of communicable disease agents and diseases; or (2) manufacturer's inability to carry out any necessary corrective action.

5. Exemptions and Alternatives (Proposed § 1271.155)

FDA recognizes the possibility that, as technology and scientific knowledge advance, new methods may be developed that could be used in the manufacture of human cellular and tissue-based products, or other unanticipated circumstances may arise that warrant a departure from an approach detailed in the regulations. Some of these technical developments may not be consistent with the terms of the donor-suitability and CGTP regulations, although the purpose of those regulations might be satisfied. In order to provide establishments with flexibility, and to ensure that the agency may respond appropriately to improved technologies and increased scientific

knowledge, the agency proposes that establishments may apply for exemptions or alternatives from the regulatory requirements contained in subparts C and D of part 1271.

Proposed § 1271.155 sets out the procedures for obtaining an exemption or alternative from a requirement in subpart C of part 1271, pertaining to donor suitability, or in subpart D of part 1271, pertaining to CGTP. Under proposed § 1271.155, an establishment could demonstrate to the agency that it should be exempted from an otherwise applicable regulatory requirement or permitted to satisfy the purpose of the requirement in an alternative manner. A request for an exemption or alternative would need to be accompanied by supporting documentation, including all relevant valid scientific data. Requests would be made in writing or electronically, except that in limited circumstances (e.g., emergencies) a request might be made and granted orally, with a written request and acknowledgment of approval to follow.

Under proposed § 1271.155(c), the Director of the Center for Biologics Evaluation and Research (CBER) could grant an exemption or alternative if he or she found that doing so would be consistent with the goals of preventing circumstances that increase the risk of the introduction, transmission, and spread of communicable disease. In addition, an exemption or alternative would be conditioned on a finding by the Director that the information submitted justified an exemption or that the proposed alternative satisfied the purpose of the requirement. An establishment that requested an exemption or alternative could not begin operating under its terms until the exemption or alternative had been granted. Some exemptions or alternatives might have expiration dates, in which case an extension could be requested. An establishment operating under the terms of an exemption or alternative would be required to maintain documentation that the exemption or alternative had been granted, and of the date on which the establishment began operating under the terms of the exemption or alternative.

B. Definitions (Proposed § 1271.3)

Definitions pertinent to part 1271 will be contained in subpart A, in § 1271.3. In the registration proposed rule, FDA set out defined terms in paragraphs (a) through (h) of § 1271.3.

In the donor-suitability proposed rule, further definitions were proposed, to be contained in § 1271.3(i) through (ee), and the proposed definition of human cellular or tissue-based product in paragraph (e) was revised.

Now, the agency is proposing new paragraphs (ff) through (tt) in § 1271.3. These new definitions are discussed below, when the requirements to which the defined terms relate are discussed.

C. Quality Program (Proposed § 1271.160)

Any establishment that manufactures human cellular or tissue-based products needs to have in place a method of ensuring that its manufacturing processes are performed properly and in compliance with applicable regulations. For devices, such a program is called a ''quality system'' (§ 820.1 *et seq.*). In these regulations, FDA is proposing to use ''quality program'' to refer to the set of activities, including management review, training, audits, and corrective and preventive actions, that represent a commitment on the part of an establishment's management to the quality of its products. FDA proposes to define ''quality program'' in § 1271.3(oo) as ''an organization's comprehensive system for manufacturing and tracking human cellular and tissue-based products. This program includes preventing, detecting, and correcting deficiencies that may lead to circumstances that increase the risk of the introduction, transmission, or spread of communicable disease.''

Proposed § 1271.160 would require an establishment that performs any step in the manufacture of human cellular and tissue-based products to establish and maintain a quality program that is appropriate for the specific human cellular and tissue-based products manufactured and the manufacturing steps performed and that meets the requirements of this part. With proposed § 1271.160, FDA intends to require that a quality program perform certain basic functions, but also intends to provide each establishment with flexibility to devise a program appropriate to its particular activities and characteristics. Thus, FDA expects that quality programs may differ from establishment to establishment, depending on the size of the establishment and the type of

manufacturing performed, among other factors. A smaller company that performs limited manufacturing steps might have a less complex quality program than a larger establishment that processes a variety of products.

Some establishments may currently have in place quality programs that would meet the requirements of proposed § 1271.160. An establishment that manufactures human cellular and tissue-based products regulated as devices would likely find it unnecessary to make major changes to its quality system established in compliance with § 820.5 in order to comply with proposed § 1271.160. Such an establishment would not need to maintain both a QS and a separate quality program.

The functions of a quality program, as listed in proposed § 1271.160(b), include but are not limited to: (1) Ensuring that required procedures are established and maintained; (2) ensuring the appropriate analysis and sharing of information that could affect the integrity and function of a human cellular or tissue-based product, possible contamination of the product, or the potential transmission of communicable disease by the product; (3) ensuring that appropriate corrective actions are taken and documented; (4) ensuring the proper training and education of personnel; (5) establishing and maintaining appropriate monitoring systems; (6) establishing and maintaining a system for maintaining records; (7) investigating and documenting product deviations and making certain required reports; and (8) conducting evaluations, investigations, audits, and other actions necessary to ensure compliance with the regulations.

Proposed § 1271.160(b)(2) would specifically require procedures to be established for sharing and receiving information that could affect the integrity and function of a human cellular or tissue-based product, the possible contamination of the product, or the potential transmission of communicable disease by the product. This would include information on testing or screening results that could make a donor unsuitable; such information would need to be shared with other establishments that are known to have recovered cells or tissue from the same donor. An establishment would also need procedures in place in order to respond appropriately (through

investigation, evaluation, possible recall, reporting, etc.) if it received any such information from another establishment.

Proposed § 1271.160(b)(7) would require establishments to investigate and document all product deviations in manufacturing. The term ''product deviation'' is defined in proposed § 1271.3(kk) as ''an event that represents a deviation from current good tissue practice, applicable standards, or established specifications; or an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease agent or disease from a human cellular or tissue-based product to a recipient, may lead to product contamination, or may adversely affect the function or integrity of the product.'' Investigation would be required to include a review and evaluation of the product deviation in manufacturing, the efforts made to determine the cause, and the implementation of corrective action designed to address the event and prevent its recurrence.

Certain product deviations in manufacturing would be required to be reported. The proposed requirement, applicable to distributed 361 products, for reporting product deviations in manufacturing that could lead to adverse reactions is discussed below in section III of this document. Certain product variations, referred to currently as errors and accidents, involving human cellular and tissue-based products regulated as biological drugs are required to be reported under 21 CFR 600.14 (currently undergoing revisions; see 62 FR 49642, September 23, 1997). In addition, each establishment would be required to perform a periodic review and analysis of all investigations of product deviations in manufacturing, at least once each year, for the purpose of identifying trends and adopting appropriate corrective and preventive measures. Section 1271.160(b)(7) specifies that this analysis shall be available for review upon inspection and for submission to FDA upon request.

Under proposed § 1271.160(c), one or more designated persons shall have authority over the quality program, and this person shall report to management at least once a year on the performance

of the quality program. However, more frequent reports may be necessary in order to keep management informed of the status of the program.

Audits are an important component of a quality program. Under proposed § 1271.160(d), a comprehensive quality audit of all activities would be required at least once a year. FDA proposes to define ''quality audit'' in proposed § 1271.3(nn), as ''a documented, independent inspection and review of an establishment's activities, including manufacturing and tracking, performed according to procedures, to verify, by examination and evaluation of objective evidence, the degree of compliance with those aspects of the quality program under review.'' In addition to the annual quality audit, special audits would be performed as necessary to ensure that quality program objectives are achieved.

Proposed § 1271.160(e) covers the use of computers or automated data processing systems used as part of the quality program, as part of manufacturing, or for maintaining manufacturing data or records. An establishment using such a computer or automated system would be required to validate the computer software for its intended use according to an established protocol, as well as all software changes. Validation and results would be required to be documented. The agency proposes to define ''validation'' in proposed § 1271.3(rr) as ''confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled * * *''.

D. Organization and Personnel (Proposed § 1271.170)

Proposed § 1271.170 sets out general requirements for the organization and personnel of establishments that manufacture human cellular and tissue-based products. Under this section, each establishment would be required to maintain an adequate organizational structure and sufficient personnel to ensure that the requirements of part 1271 are met. Moreover, an establishment would need to have sufficient personnel with the necessary education and experience, or combination thereof, to assure competent performance of their assigned functions.

Under proposed § 1271.170, personnel would only be permitted to perform those activities for which they are qualified. Training of personnel to perform their assigned responsibilities adequately would be required, as would any necessary retraining. Because of the particular risks addressed by the requirements of part 1271, the agency is proposing to require that personnel be educated about possible consequences of improperly performing their duties; e.g., the risk that an improperly handled product could cause harm to the product's recipient, by transmitting a communicable disease or by failing to function adequately. A record of the education, experience, training, and retraining would need to be maintained for all personnel.

E. Procedures (Proposed § 1271.180)

Under proposed § 1271.180, each establishment would be required to establish and maintain procedures for all significant steps that it performs in the manufacture of human cellular and tissue-based products. The agency is proposing to define ''establish and maintain'' in § 1271.3(ll) as ''define, document (in writing or electronically), and implement, then follow, review, and as needed, revise on an ongoing basis.'' FDA intends, by using the phrase ''establish and maintain'' in these regulations, to indicate that, once established, procedures must be followed on an ongoing basis. Because established procedures would, by definition, be documented in writing or electronically, the agency is proposing to use the term ''procedures'' as opposed to ''written procedures.''

Procedures required under proposed § 1271.180, and those specifically required elsewhere in subpart D of part 1271, would be required to be designed to prevent circumstances that increase the risk of the introduction, transmission, and spread of communicable diseases through the use of human cellular and tissue-based products by ensuring that: (1) The products do not contain relevant communicable disease agents; (2) the products do not become contaminated during manufacturing; and (3) the function and integrity of the products are not impaired through improper manufacturing. Procedures must be designed to ensure compliance with the requirements of part 1271.

The recovery of cells or tissue is an example of an especially significant step in the manufacture of a human cellular or tissue-based product, for which procedures would have to be established. Under the terms of proposed § 1271.180, such procedures would need to include the use of procurement techniques designed to prevent the transmission of communicable disease agents and diseases by the product. In addition, procedures for recovery would have to be designed to ensure that the function and integrity of the procured cells or tissue are maintained during and after procurement.

All procedures shall be reviewed and approved by a responsible person prior to implementation. At least once in a 12-month period, all procedures would be required to be reviewed and, if necessary, revised; such review would need to be documented. Procedures must be readily available to personnel in the area where relevant operations are performed, unless this would be impractical. Any deviation from a procedure must be authorized by a responsible person, recorded, and justified.

FDA is not prescribing the contents of particular procedures, but is allowing establishments to develop procedures that suit their particular operations. Alternatively, under proposed § 1271.180, an establishment could adopt current standard procedures, e.g., those in a technical manual prepared by another organization, so long as the procedures are consistent with the requirements of part 1271, at least as stringent as those requirements, and appropriate for the establishment's operations.

Any procedure that becomes obsolete would be required to be archived for at least 10 years. Since some tissues have long expiration dates, they can be transplanted many years after they were recovered or processed. Should an adverse reaction occur after transplantation, it would be important to know the procedures under which the tissue was recovered or processed, especially if those procedures differ from the ones currently in place.

F. Facilities, Environmental Control and Monitoring, Equipment, and Supplies and Reagents

1. Facilities (Proposed § 1271.190)

Under proposed § 1271.190, any facility used in the manufacture of human cellular or tissue-based products must be of suitable size, construction, and location to facilitate cleaning, relevant maintenance, and proper operations. A facility that, for whatever reason, cannot be adequately cleaned is not appropriate for use in the manufacture of human cellular and tissue-based products, because of the potential risk of product contamination. ''Relevant maintenance'' refers to those actions that, if not taken, could lead to potentially adverse effects on product integrity or function, or to the accidental exposure of human cellular and tissue-based products to communicable disease agents, or to contamination or cross-contamination with such agents. Finally, any operation undertaken by a manufacturing establishment needs to be performed in a facility in which the operation can be performed correctly. For example, although not specifically required to do so by these regulations, an establishment may need to establish gowning procedures for its employees, in order that their functions be performed properly. Such an establishment would need to provide employees with a dressing room and gowning area.

Proposed § 1271.190 would also require that a facility be maintained in a good state of repair. Broken windows, peeling paint, uneven flooring, and improper electrical wiring are all examples of maintenance problems that could lead to product contamination or impairment of product function or integrity. In addition, adequate lighting, ventilation, plumbing, drainage, and washing and toilet facilities would all be required.

Proposed § 1271.190(b) sets out requirements for the location of operations within a facility used in the manufacture of human cellular or tissue-based products. Such a facility would need to be divided into separate or defined areas of adequate size for each operation that takes place in the facility. As an alternative, however, other control systems could be established and maintained to prevent improper labeling, mix-ups, contamination, cross-contamination, and accidental exposure of human cellular and tissue-based products to communicable disease agents. Examples of different types of operations that an establishment might perform, and which would need to be conducted either in separate locations or subject to other controls, include: (1) Receipt,

identification, and storage of containers, labels, supplies, and reagents; (2) processing, including laboratory functions; (3) storage of human cellular and tissue-based products, both before and after release from quarantine; (4) product labeling; (5) storage and disposal of biohazards and/or medical waste; (6) irradiation; and (7) sterilization and aseptic processing.

Proposed § 1271.190(c) contains basic requirements for facility cleaning and sanitation. Facilities must be maintained in a clean, sanitary, and orderly manner. Sewage, trash, and other refuse must be disposed of in a timely, safe, and sanitary manner. Procedures for facility cleaning and sanitation would be required to be established and maintained. These procedures would need to include an assignment of responsibility for sanitation, cleaning methods to be used, and a cleaning schedule. Finally, all significant cleaning and sanitation activities that are done to prevent contamination would need to be documented, and records maintained.

2. Environmental Control and Monitoring (Proposed § 1271.195)

Proposed § 1271.195 would require monitoring and control over environmental conditions where such conditions (e.g., temperature, air quality) could reasonably be expected to have an adverse effect on the function or integrity of human cellular and tissue-based products, to cause contamination or cross-contamination of products or equipment, or to lead to accidental exposure of products to communicable disease agents. In these situations, an establishment would be required to establish and maintain procedures to adequately control and monitor environmental conditions and to provide proper conditions for operations.

Depending on the particular environmental factors at a facility, and the type of operations that take place there, environmental controls and monitoring could include one or more of the following: Temperature and humidity controls; ventilation and air filtration; cleaning and disinfecting of rooms and equipment to ensure aseptic processing operations; maintenance of equipment used to control conditions necessary for aseptic processing operations; and environmental monitoring for organisms. Proposed § 1271.195(a) would require these elements to be adopted, where appropriate. Thus, under proposed § 1271.195, an establishment would be required first to

identify any environmental conditions that require monitoring and control, and then to respond appropriately.

Periodic inspections of environmental controls systems would be required. In addition, environmental controls and monitoring activities would have to be documented, and records maintained.

3. Equipment (Proposed § 1271.200)

CGTP requirements for equipment are set out in proposed § 1271.200. For human cellular and tissue-based products to be manufactured properly, the equipment used in their manufacture must be appropriate. Thus, § 1271.200(a) contains the general requirement that equipment used in the manufacture of human cellular and tissue-based product be of appropriate design for its use. Equipment must be suitably located and installed to facilitate operations, including cleaning and maintenance. In addition, equipment must not have any adverse effect on the products being manufactured.

Equipment used for inspection, measuring, and testing must be capable of producing valid results; such equipment could include automated, mechanical, electronic, computer, or other kinds of equipment. Section 1271.200(c) would require regularly scheduled calibration of equipment used for inspection, measuring, and testing. Thus, for example, a thermometer used in a storage area would be required to produce valid results and would also be subject to regularly scheduled calibration procedures. ''Equipment used for inspection'' would include any equipment used to inspect a human cellular or tissue-based product during its manufacture or prior to making it available for distribution.

Under § 1271.200(b), an establishment would be required to establish and maintain procedures for cleaning, sanitizing, and maintaining equipment. The purpose of these procedures is to prevent equipment malfunctions, contamination or cross-contamination, accidental exposure of human cellular and tissue-based products to communicable disease agents, and other events that could reasonably be expected to have an adverse effect on product function or integrity. Cleaning,

sanitizing, and maintenance of equipment would be required to be performed according to established schedules.

Section 1271.200(d) sets out a requirement for routine inspections of equipment for cleanliness, sanitation, and calibration, and to ensure compliance with maintenance schedules.

Section 1271.200(e) contains specific requirements for records, to be maintained in accordance with the general records provisions in § 1271.270. All maintenance, cleaning, sanitizing, calibration, and other activities performed in accordance with § 1271.200 would be required to be documented. Records of recent maintenance, cleaning, sanitizing, calibration, and other activities must be available at each piece of equipment; this requirement promotes both accurate recordkeeping and ease of reference. In addition, the use of each piece of equipment must be documented, and this record of use must identify each human cellular or tissue-based product manufactured using the equipment. This requirement is necessary to ensure that those products manufactured with a particular piece of equipment may be traced for follow-up and appropriate corrective action, in the event that a problem (e.g., contamination or malfunction) is discovered after the equipment is used.

4. Supplies and Reagents (Proposed § 1271.210)

Use of a contaminated or otherwise defective supply or reagent in the manufacture of a human cellular or tissue-based product could adversely affect the product; e.g., by introducing a disease agent or by failing to properly preserve the product. For this reason, compliance with CGTP requires that care be taken in receiving supplies and reagents into an establishment, in determining their appropriateness for use, and in keeping track of the products in whose manufacture they are used. By ''supplies and reagents,'' the agency refers to all of the products that might be used during the manufacturing process but excludes any material that might be considered to become a component of a human cellular or tissue-based product. Supplies and reagents would include, but not be limited to, ''processing material,'' which the agency is proposing to define at § 1271.3(hh) as ''any material or substance that is used in, or to facilitate, processing, but which

is not intended by the manufacturer to be included in the human cellular or tissue-based product when it is made available for distribution.''

Proposed § 1271.210 contains several requirements with respect to supplies and reagents used in the manufacture of human cellular and tissue-based products. An establishment would be required to establish and maintain procedures for receiving supplies and reagents. Before using a supply or reagent, the establishment must verify that the supply or reagent meets specifications that are designed to prevent circumstances that increase the risk of the introduction, transmission, and spread of communicable disease through product contamination or the impairment of product function or integrity. An establishment could verify on its own that the supplies and reagents that it uses meet specifications; e.g., by testing the product. Alternatively, verification could be accomplished by the vendor of the supply or reagent. ''Verification'' is defined in proposed § 1271.3(ss) as ''confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.''

Section 1271.210(b) would require that reagents used in processing and preservation of human cellular and tissue-based products be of appropriate grade for their intended use and, if appropriate, sterile. Some establishments may produce their own in-house reagents. These establishments would be required to validate and/or verify the procedures for producing such reagents.

Section 1271.210(c) would require that specific records relating to the receipt, verification, and use of each supply and reagent be maintained.

G. Processing

Three sections of the proposed CGTP regulations address the processing of human cellular and tissue-based products. Proposed § 1271.220 would require controls to be established over processing. Requirements for making changes to processes are contained in proposed § 1271.225. Proposed § 1271.230 would require process validation in place of verification in some situations and sets out certain specific requirements related to process validation.

''Processing'' is defined in proposed § 1271.3(mm) as ''any activity other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution performed on a human cellular or tissue-based product, including, but not limited to, preparation, sterilization, steps to inactivate and remove adventitious agents, preservation for storage, and removal from storage.''

1. Process Controls (Proposed § 1271.220)

Under proposed § 1271.220(a), any establishment engaged in the processing of human cellular and tissue-based products would be required to develop, conduct, control, and monitor its manufacturing processes to ensure that each product: (1) Conforms to its specifications, (2) is not contaminated, (3) maintains its function and integrity, and (4) is manufactured so as to prevent transmission of communicable disease by the product. By ''specifications,'' the agency refers to those criteria established by a manufacturer for a human cellular or tissue-based product that must be met at defined stages in the manufacturing process and before the product is made available for distribution.

Sections 1271.220(b) governs the removal of processing materials. In accordance with the definition proposed in § 1271.3(hh), processing materials would not be intended by the manufacturer to be included in a human cellular or tissue-based product when it is made available for distribution. Under § 1271.220(b), where a processing material could reasonably be expected to have an adverse effect on a human cellular or tissue-based product's function or integrity, the establishment would be required to establish and maintain procedures for the use and removal of the processing material to ensure that it is removed or limited to an amount that does not adversely affect the product's function or integrity. Any such removal or reduction would be required to be documented.

Section 1271.220(c) would prohibit the pooling of human cells or tissue from two or more donors during manufacturing. Pooling refers to placing products in physical contact with each other or mixing them in a single receptacle. Such commingling of cells or tissues from a single infected donor with cells or tissues from other donors can contaminate the entire pooled quantity, greatly increasing the risk to recipients of the pooled materials of exposure to infectious agents. The

proposed regulation is consistent with recommendations made by FDA's Transmissible Spongiform Encephalopathy Advisory Committee, at their meeting on October 6, 1997, with respect to the pooling of dura mater.

Section 1271.220(d) would require procedures to be established for in-process monitoring, or monitoring of the product during processing, for compliance with specified requirements. This requirement is modified by the phrase ''where appropriate.'' In other words, as discussed in section II.A.4. of this document, in-process monitoring would be required unless the establishment can justify, and document, that it would be unnecessary under the terms of § 1271.150(d). The in-process product would have to be controlled until the completion of any required inspection, tests, or other verification activities, or until any necessary approvals are received and documented. Any sampling taken of the in-process product for the purpose of testing or inspection would be required to be representative of the material being evaluated.

2. Process Changes (Proposed § 1271.225)

Proposed § 1271.225 would require an establishment to establish procedures for making changes to a process. Any such change would have to be verified or validated, to ensure that the change does not create an adverse impact elsewhere in the operation. Any change would also have to be approved by a responsible person with appropriate knowledge and background before being implemented. Proposed § 1271.225(b) would require that records be kept of all such changes, and sets out the required elements of such records (e.g., the rationale for the change).

3. Process Validation (Proposed § 1271.230)

Proposed § 1271.230 contains requirements related to the validation of processes. Process validation, under proposed § 1271.3(rr), means ''establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.''

Proposed § 1271.230(a) would require establishments to validate their processes where verification is not feasible; e.g., where verification cannot be performed on each and every finished product. Thus, § 1271.230(a) states that, where the results of a process cannot be fully verified

by subsequent inspection and tests, the process must be validated and approved according to established procedures, and the validation activities must be documented.

Under § 1271.230(b), any claim made in labeling or promotional materials that is related to the process used to manufacture a human cellular or tissue-based product must be based on a process that has been validated. Validation must be documented, and evidence of the validation must be maintained at the establishment and made available for review on inspection. Examples of such process-related claims include the claim that a product is sterile or that it has undergone viral inactivation.

The agency is proposing in § 1271.230(c) a requirement that would apply specifically to establishments that process dura mater. Donor screening and testing requirements for donors of dura mater have been proposed in the donor-suitability proposed rule, but additional processing safeguards are necessary to prevent the transmission of Creutzfeldt-Jakob disease (CJD) (64 FR 52696 at 52706). Proposed § 1271.230(c) would require that dura mater be processed using a validated procedure to reduce CJD infectivity, while preserving the clinical utility of the product. Currently, an example of such a procedure would be a sodium hydroxide (NaOH) protocol that has been validated to reduce CJD infectivity (in an animal model) while preserving the tissue's clinical utility. In the future, other methods that more effectively reduce CJD infectivity may be developed.

If processes are validated, in place of verification, then procedures must be established and maintained to ensure that the specified requirements continue to be met; this requirement appears in proposed § 1271.230(d). Under § 1271.230(e), any change or deviation from a validated process would require a review and evaluation of the process and, where appropriate, revalidation.

H. Labeling Controls (Proposed § 1271.250)

Under proposed § 1271.250, an establishment would be required to establish and maintain procedures to control the labeling of human cellular and tissue-based products. These control procedures would be designed to ensure that products are identified properly and to prevent mix-

ups. The agency is not specifying how such controls should be designed, but notes that they would likely need to include such elements as proper storage methods to prevent deterioration of adhesives, among other problems. In addition, § 1271.250 would require procedures to include verification of label accuracy, legibility, and integrity. Thus, for example, a labeled product would be checked under such verification procedures to ensure that its label was affixed securely to the container, could be read with ease, and accurately identified the product by identifier and product type.

Proposed § 1271.250 would also require that procedures be established and maintained to ensure that products are labeled in accordance with all applicable labeling requirements. ''Applicable labeling requirements'' for human cellular and tissue-based products regulated as biological drugs include the labeling regulations in parts 201 and 610 (21 CFR parts 201 and 610); for products regulated as devices, they include those in part 801 (21 CFR part 801). Other labeling requirements appear in several sections of proposed part 1271, and these are listed in proposed § 1271.250. For example, § 1271.90 is cross-referenced in § 1271.250; it would require that banked cells and tissues for autologous use be labeled ''FOR AUTOLOGOUS USE ONLY'' (donor-suitability proposed rule (64 FR 52723)). Procedures established in compliance with proposed § 1271.250 would need to ensure that banked cells and tissues for autologous use were labeled with this statement.

I. Storage (Proposed § 1271.260)

Proposed § 1271.260 sets out storage requirements. The proposed regulation addresses three general areas of concern: Control of storage areas; storage temperature; and expiration date.

Under proposed § 1271.260, each establishment would be required to establish and maintain procedures for the control of storage areas and stock rooms in order to prevent mix-ups, commingling, deterioration, contamination, and cross-contamination of human cellular and tissue-based products and supplies, as well as any other condition that might adversely affect product

function or integrity. In addition, controls would be required to prevent improper release for distribution.

Storage at a proper temperature, in order to preserve a product's function and integrity and prevent deterioration, is an important aspect of CGTP. FDA recognizes that appropriate temperatures may differ for various types of products. Thus, § 1271.260(b) would require an establishment to establish acceptable temperature limits for the storage of human cellular and tissue-based products at each step of the manufacturing process. Monitoring of storage temperatures would be required. Temperatures would have to be documented, and recorded temperatures reviewed periodically to assure that temperatures remained in the permissible range.

Different products may be stored for differing lengths of time before use. The maximum storage period depends on such factors as product type, processing procedures and method of preservation, storage conditions, and type of packaging. Section 1271.260(c) would require, where appropriate, that an expiration date be assigned for each human cellular or tissue-based product.

Under § 1271.260(d), corrective action must be taken and documented whenever proper storage conditions are not met.

J. Receipt and Distribution (Proposed § 1271.265)

Proposed § 1271.265 covers the receipt and distribution of human cellular and tissue-based products. Section 1271.265(a) contains general requirements for procedures and recordkeeping. Section 1271.265(b) governs receiving activities. Requirements that must be met prior to making a product available for distribution are contained in § 1271.265(c). The remaining paragraphs deal with packaging, shipping conditions, and the return of products to inventory.

Under § 1271.265(a), procedures would be required for receiving, accepting or rejecting, and distributing human cellular and tissue-based products, as well as for the destruction or other disposition of such products. Each of these activities, when performed, must be documented. Required documentation would include the identification of the human cellular or tissue-based product, the activities performed and the results of such activities, the date or dates of the activity,

the quantity of product subject to the activity, and the disposition of the product. The disposition of the product would include, for example, the identity of the consignee. Complete and accurate identification of a consignee would include not only the consignee's name, but its address and telephone number.

Section 1271.265(b) contains specific requirements with respect to the receipt of human cellular and tissue-based products for processing, distribution, or any other step in the manufacturing process. As part of its receiving activities, an establishment would be required to inspect incoming human cellular and tissue-based products, according to established procedures, for damage, contamination, deterioration, or any other indication that the integrity of the product had been impaired. The establishment would then determine whether to accept or reject the product. Acceptance or rejection of the incoming product would need to be documented.

An establishment receiving a human cellular or tissue-based product would also be required to ascertain its status and handle the product appropriately. For example, a product that is shipped under quarantine, pending completion of the donor-suitability determination required under subpart C of part 1271, would be required to be maintained in quarantine after its receipt until the determination was complete. Other issues of product status (e.g., stage in processing, results of donor screening and testing) would dictate other appropriate action with respect to the product.

Proposed § 1271.265(c) deals with an establishment's determination that a product is ''available for distribution,'' a term that the agency is proposing to define in proposed § 1271.3(ff). Under that definition, a human cellular or tissue-based product is ''available for distribution'' if it has been determined to meet all release specifications and to be suitable for distribution. Under § 1271.265(c), an establishment would be required to establish and maintain procedures for making products available for distribution, including developing release criteria. These procedures would be designed to prevent the release of products that are in quarantine, have deteriorated, or otherwise have been manufactured in violation of CGTP. They must also prevent the release of products

from donors who have not been determined to be suitable, except as provided under proposed §§ 1271.65 and 1271.90.

Prior to making a human cellular or tissue-based product available for distribution, an establishment would be required to review all records pertaining to the product and to verify and document that release criteria have been met. The determination that a product is available for distribution must be documented and dated by a responsible person.

Under § 1271.265(d), all packaging and shipping containers would be required to be designed, validated, and constructed so as to ensure product function and integrity and to protect the product from damage, deterioration, contamination, or other adverse effects during customary conditions of processing, storage, handling, and distribution. Section 1271.265(e) would require that appropriate shipping conditions, to be maintained during transit, be defined for each type of product. And § 1271.265(f) would require that an establishment develop procedures for determining whether a product that is returned to the establishment may be returned to inventory.

K. Records (Proposed § 1271.270)

Proposed § 1271.270 contains general requirements for recordkeeping under part 1271. Section 1271.270(a) would require establishments to maintain records concurrently with the performance of each significant step required in subparts C and D of part 1271. Many, but not necessarily all, of the requirements for documenting a manufacturing activity are specifically noted elsewhere in the regulations. For example, an establishment's receipt of tissue for processing would be a significant step that needs to be documented; proposed § 1271.265(a) lists the specific documentation that would be required. As noted in proposed § 1271.270(a), any requirement in part 1271 that an activity be documented involves the creation of a record, and that record would be subject to the requirements of § 1271.270.

Section 1271.270(a) would require records to be accurate, indelible, and legible. Entries must be dated and the person performing the work in question must be identified. Records would have to be sufficiently detailed to provide a complete history of the work performed and to relate the

records to the particular human cellular or tissue-based product involved. In order to protect the privacy of both donors and recipients, adequate record security systems would be required.

Under § 1271.270(b), establishments would have the flexibility to develop individualized systems of maintaining and organizing their records, so long as certain objectives were achieved. Records could be maintained in more than one location, provided that the records management system was designed to ensure prompt identification, location, and retrieval of all records. Further, the records management system would need to facilitate the review of a particular human cellular or tissue-based product's history both prior to its release for distribution and, if necessary, at a later date as part of a follow-up evaluation or investigation. In addition to records pertaining to individual products, records for product types would be required to be maintained and organized. Thus, for example, a manufacturer of several different types of human cellular and tissue-based products would be required to maintain, for each product type, records of pertinent procedures, product specifications, labeling and packaging procedures, and equipment logs. A records management system could be as simple as keeping all information pertaining to the manufacture of one product in one file folder, and keeping all file folders for one product type, e.g., tendons, in one drawer of the file cabinet. This drawer, labeled ''Tendons'', would also contain a folder for ''generic'' procedures common to all tendons. A more elaborate records management system could utilize a computer to generate files and subfiles.

Section 1271.270(d) and (e) deal with methods and time frames for retaining records. Under § 1271.270(d), records could be maintained electronically, as original paper records, or as true copies. Examples of true copies include photocopies, microfiche, and microfilm. Suitable equipment would be required to be available for reading and photocopying any records maintained on microfiche or microfilm. Records stored in automated data processing systems must be backed up to prevent their loss. Any electronic record or electronic signature would be subject to the requirements in 21 CFR part 11.

Under § 1271.270(e), all records would be required to be kept for 10 years after their creation. However, consistent with proposed § 1271.55(b) on records of donor-suitability determinations, records pertaining to a particular human cellular or tissue-based product must be retained at least 10 years after the date of implantation, transplantation, infusion, or transfer of the product. See donor-suitability proposed rule (64 FR 52721). If the date of implantation, transplantation, infusion, or transfer is not known, then the records must be retained at least 10 years after the date of the product's distribution, disposition, or expiration, whichever is latest. The establishment must make provisions for all records to be maintained for the required period in the event that the establishment ceases operation. FDA requests comment on whether there are specific types of records for which a retention period shorter than 10 years would be appropriate and would not compromise the agency's ability to prevent the introduction, transmission and spread of communicable disease.

Section 1271.270(c) cross-references records requirements proposed in subpart C of part 1271 that relate to donor testing and screening, in order to make clear that records required under subpart C of part 1271 are subject to the recordkeeping requirements in § 1271.270. Section 1271.270(f) would require an establishment to maintain records of contracts, agreements, and other arrangements with other establishments under which any step in the manufacturing process is performed by the other establishment. These records would need to contain not only the name and address of the other establishment, but also a description of each party's responsibilities.

L. Tracking (Proposed § 1271.290)

FDA considers product tracking to be an essential component of its proposed regulatory system for human cellular and tissue-based products. Should the recipient of such a product contract a communicable disease, tracking would permit appropriate follow-up, such as an investigation to determine whether the human cellular or tissue-based product transmitted the disease agent and, if so, would permit steps to be taken to prevent the distribution of other similarly infected products. Similarly, if a donor is discovered, post-donation, to have had a communicable disease, tracking

would permit an establishment to locate products from that donor. Thus, a tracking system is closely linked to the agency's regulatory objective of preventing the spread of communicable disease.

As with other components of these CGTP regulations, FDA is proposing certain basic requirements, but is allowing establishments flexibility in designing tracking programs that suit their particular activities. Auditing of an establishment's tracking method to ensure its effectiveness would be required under the quality program (proposed § 1271.160(b)(8) and (d)). FDA recognizes that some establishments have already developed and implemented tracking systems and requests comments from those establishments on the success or failure of particular tracking methods.

Part 821 (21 CFR part 821) of FDA's regulations contains the medical device tracking requirements. Except for dura mater, human cellular and tissue-based products regulated as devices generally have not been subject to tracking under part 821; thus, there will be little or no duplication of tracking requirements. When a human cellular or tissue-based product is designated as a ''tracked device,'' and subject to the device tracking regulations, the manufacturer would be required to satisfy both sets of tracking requirements. However, given the variety of methods that could be devised to satisfy the tracking requirements proposed in § 1271.290, it is foreseeable that a single tracking method could be adopted that conforms with the requirements of both § 1271.290 and part 821.

Proposed § 1271.290 would require each human cellular or tissue-based product to be tracked. Section 1271.290(a) would place the tracking obligation on each establishment that performs any step in the manufacture of a human cellular or tissue-based product.

Proposed § 1271.290(b) would require the establishment to establish and maintain a method of product tracking that enables the tracking of all human cellular and tissue-based products from the donor to the recipient or final disposition and conversely from the recipient or final disposition to the donor. FDA recognizes, however, that some establishments may be better equipped than others to establish an effective tracking system. For this reason, the agency proposes to permit an establishment that performs some, but not all, of the steps in the manufacturing process to

participate in a method of product tracking that has been established by another establishment responsible for other steps in the manufacturing process, provided that the tracking method meets all the requirements of § 1271.290. One possible method of tracking would be to collect information about recipients on cards that are returned to the tracking establishment.

Section 1271.290(c) would require that each human cellular or tissue-based product be assigned and labeled with a distinct identification code (e.g., alphanumeric) that relates the product to the donor and to all records pertaining to the product. Except in the case of autologous or directed donations, such a code must be created specifically for tracking and may not include an individual's name, social security or medical record number. An establishment that receives a human cellular or tissue-based product for further manufacturing might use the code already assigned or might assign a new identifier to the product. The regulation specifies, however, that an establishment that assigns a new identifier to a product shall establish and maintain procedures for relating the new identifier to the old identifier.

Section 1271.290(d) would require establishments to ensure, through agreements with consignees or through other measures, that the code and type of each human cellular or tissue-base product that is implanted, transplanted, infused, or transferred into a recipient be recorded in the recipient's medical records, or in other pertinent records, to enable tracking from the recipient to the donor. Section 1271.290(e) would require an establishment to document and maintain records of the disposition of each of its human cellular or tissue-based products to enable tracking from the donor to the recipient or final disposition. The information to be maintained must permit the prompt identification of the recipient of the product.

Under § 1271.290(f), an establishment would be required to inform its consignees in writing of the requirements in § 1271.290 and of the tracking method that the establishment is using to comply with those requirements. For example, a statement might be included in the materials accompanying the consigned human cellular or tissue-based product that would describe applicable regulations and the establishment's tracking method. The establishment would be required to

document that the consignee agreed to participate in its tracking method and to take all necessary steps to ensure compliance with the requirements of § 1271.290; this agreement would need to be obtained and documented upon initial distribution of human cellular or tissue-based products to a consignee and would not need to be obtained for each subsequent consignment.

Proposed § 1271.290(g) contains a requirement specific to donors of dura mater, intended to address the particular communicable-disease concerns associated with that type of product. Appropriate specimens from the dura mater donor would be required to be archived, under appropriate storage conditions, and for the appropriate duration, to enable future testing of the archived material for evidence of transmissible spongiform encephalopathy (TSE) and appropriate disposition of any affected dura mater tissue, if necessary. Although archiving samples may not immediately increase the assurance of safety for a dura mater graft, it would permit later testing for TSE-induced changes using improved or new methods as they become available. In the event that a dura graft recipient became ill with CJD, such testing of archival donor material would be needed to confirm whether the dura graft was the source of infection, so that no additional grafts from the affected lot would be distributed. At this time, based on currently available information, FDA recommends that samples of donor brain and dura mater tissues be archived at a temperature equal to or less than minus 70 °C for 16 years beyond the product's expiration date.

Ideally, archived samples should be retained for the lifetime of the graft recipient, because the maximum incubation period is not certain. To date, the longest known incubation period is 16 years (Ref. 1). FDA believes that it may be unrealistic to expect a manufacturer to maintain an archive for such a long time. FDA suggests that establishment of a nationally supported archive be considered for prolonged storage of these materials, in order to further the study of iatrogenic transmission of spongiform encephalopathies.

M. Complaint Files (Proposed § 1271.320)

Proposed § 1271.320 would require establishments to maintain records of, and review, all complaints. ''Complaint'' is defined in proposed § 1271.3(ii) as:

any written, oral, or electronic communication that alleges: (1) that a human cellular or tissue-based product has transmitted or may have transmitted a communicable disease to the recipient of the product; (2) that the function or integrity of a human cellular or tissue-based product may have been impaired; or (3) any other problem with a human cellular or tissue-based product that could result from the failure to comply with current good tissue practice.

A communication from a physician expressing concern about possible product contamination would be a ''complaint.''

The proposed regulation would require establishments to establish and maintain procedures for the prompt review, evaluation, and documentation of all complaints. Records of each complaint that the establishment receives would be required to be maintained in a file designated for complaints. The complaint file would be required to contain sufficient information about each complaint for proper review and evaluation of the complaint, including the identifier of the human cellular or tissue-based product that is the subject of the complaint. For example, the complaint file should include the date of each report, the unique product identifier, and the name of the person or establishment that submitted the complaint. Proposed § 1271.320 would require that the complaint file be made available for review and copying upon request from an authorized employee of FDA. Section 1271.320(c) sets out requirements for the review and evaluation of complaints.

III. Additional Requirements With Respect to 361 Products

Proposed subpart E of part 1271 contains reporting and labeling requirements that would apply only to those establishments that manufacture human cellular and tissue-based products as described in proposed § 1271.10 (registration proposed rule (63 FR 26754)). Such products would be products that: (1) Are minimally manipulated, (2) are not promoted or labeled for any use other than a homologous use, (3) are not combined with or modified by the addition of any nontissue or

noncellular component that is a drug or a device, and (4) do not have a systemic effect. The agency proposes to regulate such products solely under the authority of section 361 of the PHS Act and not as biological drugs or devices. Thus the heading of subpart E of part 1271 is ''Additional Requirements for Establishments Described in § 1271.10.'' Human cellular and tissue-based products regulated as biological drugs or as medical devices will continue to be subject to reporting and labeling requirements that are currently in place.

Although the title of proposed subpart E of part 1271 refers to ''additional'' requirements for establishments described in § 1271.10, the proposed reporting and labeling requirements are designed to be less extensive and burdensome than the current requirements applicable to products regulated as biological drugs or as devices. This approach is in keeping with the agency's expressed plans to put in place a tiered regulatory scheme, under which human cellular and tissue-based products would be subject to an appropriate level of regulation based on the degree of risk. At the same time, the proposed reporting and labeling requirements for 361 products have been drafted to be generally consistent with existing biological drug and device regulations.

A. Reporting Requirements (Proposed § 1271.350)

In order to stay informed of potential problems with human cellular and tissue-based products related to communicable-disease transmission, and to be able to take appropriate steps in response, FDA needs to receive information from establishments on adverse reactions and certain product deviations that could result in adverse reactions. For this reason, FDA is proposing to require two different kinds of reports from establishments that manufacture human cellular and tissue-based products regulated solely under section 361 of the PHS Act: the reporting of adverse reactions, and the reporting of product deviations.

1. Adverse Reactions

Under proposed § 1271.350(a), establishments would be required to report adverse reactions to CBER. The agency is engaged in an ongoing effort to enhance agency-wide consistency in the collection of safety data and, where possible, consistency with the definitions, reporting periods,

formats, and standards recommended by the International Conference on Harmonisation of Technical Requirements of Registration of Pharmaceuticals for Human Use (ICH). See ''Expedited Safety Reporting Requirements for Human Drug and Biological Products,'' final rule (62 FR 52237, October 7, 1997). In order to achieve a degree of uniformity throughout the agency and to simplify reporting requirements for firms, FDA has modeled the procedures in § 1271.350(a) on the reporting requirements for other regulated products (i.e., drugs, devices, and biological products) and is proposing to require use of the same standard reporting form that is already in use (FDA Form-3500A).

Proposed § 1271.3(gg) would define an adverse reaction as ''a noxious and unintended response to any human cellular or tissue-based product for which there is a reasonable possibility that the response may have been caused by the product (i.e., the relationship cannot be ruled out).'' This definition reflects the agency's intention to shift from adverse experience reporting to adverse reaction reporting, consistent with ICH guidelines (62 FR 52237 at 52238), and is consistent with the ICH E2A guideline's definitions of ''adverse drug reaction,'' International Conference on Harmonisation; Guideline on Clinical Safety Data Management; Definitions and Standards for Expedited Reporting, availability (60 FR 11284 at 11285, March 1, 1995). Under the proposed definition, not all unsuccessful outcomes would be considered ''adverse reactions.'' For example, the agency recognizes that a recipient may reject a human cellular or tissue-based product, or that there may be a failure to engraft (e.g., of hematopoietic stem cells), for reasons that are unrelated to the product itself. Or a procedure may fail for reasons that, whether or not specifically identified, are known not to be product-related. On the other hand, if the relationship between the product and the noxious and unintended response cannot be ruled out, the response would be considered an adverse reaction under the proposed definition.

The phrase ''the relationship cannot be ruled out'' is included in the proposed definition to clarify which individual cases should be reported to FDA. Instances of probable, possible, remote, or unlikely relationships would all be considered adverse reactions, because there would be at

least a reasonable possibility that the noxious and unintended response may have been caused by the human cellular or tissue-based product, even though causality has not been established.

Under proposed § 1271.350(a), only those adverse reactions that involved the transmission of a communicable disease, product contamination, or the failure of a human cellular or tissue-based product's function or integrity would be required to be reported. Moreover, reporting would be limited to those adverse reactions that are fatal or life-threatening, that result in permanent impairment of a body function or permanent damage to body structure, or that necessitate medical or surgical intervention.

In order to determine which adverse reactions are required to be reported, each establishment would be required to review all adverse reaction reports. The source of the information is not relevant; all reports, regardless of source, would have to be considered.

The procedures proposed for reporting adverse reactions are modeled on those used for other products regulated by the agency. Reports to the agency would be required within 15 calendar days of initial receipt of the information, with a possible follow-up report. Reports would be submitted to CBER. The proposed regulation provides addresses and information on obtaining forms.

With respect to human cellular and tissue-based products regulated as biological drugs, the reporting requirements in 21 CFR 600.80 continue to apply. For those products regulated as devices, the medical device reporting requirements in 21 CFR part 803 apply. The agency notes that the transmission of a serious communicable disease would constitute an event that is required to be reported under current regulations.

2. Product Deviations

FDA is proposing to require, in § 1271.350(b), that those product deviations that could reasonably be expected to lead to a reportable adverse reaction be reported to CBER, along with information on corrective actions. A definition of the term ''product deviation'' is proposed in § 1271.3(kk) and has been discussed at section II.C of this document.

In the proposed approach document, FDA indicated that establishments would be required to maintain records of errors and accidents, a term that is incorporated in this proposal within the meaning of ''product deviation'' (see proposed § 1271.3(kk)), and to make them available for inspection, but that no reports to the agency would be required. The General Accounting Office, in its report on human tissue banks, criticized the agency for not requiring that such records be reported (Ref. 2) .

The agency is now proposing to require the reporting of certain product deviations: those that are of the type that could reasonably be expected to lead to a reportable adverse reaction. In addition, required reporting would be limited to product deviations involving human cellular or tissue-based products that have been distributed. The agency considers that these limitations on the reporting obligation will lessen the burden on establishments and on the agency, making it possible for the agency to receive meaningful information and respond appropriately (e.g., by monitoring recalls and assisting in their implementation as necessary and appropriate).

Proposed § 1271.350(b) sets out the requirements for reporting product deviations that could give rise to an adverse reaction and provides the address to be used. Reports of such product deviations would be expected as soon as possible. Although no particular reporting form would be required, § 1271.350(b)(2) states that each report shall contain a description of the product deviation and information on all corrective actions that have been or will be taken in response to the product deviation, such as recalls.

B. Labeling and Claims

Proposed § 1271.370 contains requirements for product labeling and would govern promotional claims made for human cellular and tissue-based products regulated solely under the authority of section 361 of the PHS Act. Section 1271.370(a) describes the required contents of product labels and accompanying materials. The types of claims that may be made for human cellular and tissue-based products are addressed in § 1271.370(b).

The agency considers regulation of labeling and promotion to be an essential part of its proposed tiered, risk-based regulatory system for human cellular and tissue-based products.

Labeling and promotional materials which contain incomplete, unclear, inaccurate, unbalanced, or misleading information can increase the risk of the introduction, transmission, or spread of communicable disease by misleading the public into inappropriate or unsafe practices regarding these products (e.g., storing a product at an incorrect temperature) or by hindering corrective action which might become necessary (e.g., by delaying identification of the establishment distributing an unsafe product).

For these reasons, the agency considers that section 361 of the PHS Act provides the agency with sufficient authority to issue these requirements.

1. Labeling Information

Proposed § 1271.370(a) would require each human cellular or tissue-based product made available for distribution to be labeled clearly and accurately. In addition, certain basic information would be required to appear on the product label: (1) The name and address of the establishment that determined that the product met release criteria and made the product available for distribution, (2) a description of the type of product, and (3) the product's expiration date, if any. The agency considers each of these items to be of sufficient importance that they warrant placement on the product label itself instead of in materials that accompany the product. The first two items are crucial for accurately identifying the product and responsible establishment in the event of any necessary follow-up action (e.g., adverse reaction reports). Requiring products to be labeled with their expiration dates helps to ensure that they maintain their function and integrity at the time of use.

Recognizing that space on the product label may be limited, the agency proposes to require that the following information appear either on the product label or in a package insert: (1) Storage temperature, (2) warnings, where appropriate, and (3) instructions for use. Information on storage temperature will help prevent errors in handling and help ensure that the product maintains its

integrity and functions properly in the recipient. Warnings and instructions for use will inform the physician of the proper use of the product and would increase the probability of a successful procedure.

2. Claims

Section 1271.370(b) deals with claims for human cellular and tissue-based products in labeling, advertising, and promotional materials. Consistent with the agency's plans outlined in the proposed approach document, this provision would require that any such claim be clear, truthful, balanced, and not misleading. A ''balanced'' claim for a product would, for example, reflect an objective, unbiased view of the product, including not only claims for the product's benefits but also explanations of any hazards. A claim may be considered to be misleading if it omits important information.

Proposed § 1271.370(b)(2) is intended to clarify one of the four criteria that must be met for a human cellular or tissue-based product to be regulated solely under the authority of section 361 of the PHS Act. Under proposed § 1271.10, a 361 product is one that, in addition to meeting other criteria, is not promoted or labeled for any use other than a homologous use (registration proposed rule (63 FR 26744 at 26754)). Section 1271.370(b)(2) explains that a labeling claim or promotional materials regarding the therapeutic or clinical outcome of a human cellular or tissue-based product (other than for reconstruction, replacement, repair, or supplementation of cells or tissue) would be considered a claim for a use other than a homologous use. A product for which such a claim was made would be subject, along with its labeling, to regulation under the act and/or section 351 of the PHS Act.

3. Labeling of Biological Drugs and Devices

Proposed § 1271.370 applies only to 361 products; human cellular and tissue-based products regulated as biological drugs or as devices will continue to be subject to labeling requirements currently in place. Parts 201 and 610 (21 CFR parts 201 and 610) will apply to human cellular or tissue-based products regulated as biological drugs, as will relevant statutory provisions and

any conditions of product licensure. Human cellular and tissue-based products regulated as devices will be subject to the labeling requirements in part 801, in addition to the provisions of the act and any applicable conditions of approval or clearance.

In order to ensure that all human cellular and tissue-based products, regardless of regulatory category, bear certain basic relevant information, FDA proposes to interpret several current regulations as encompassing the information set out in proposed § 1271.370(a). The agency would expect the information listed in proposed § 1271.370(a) to appear on the label or package insert of those products regulated as biological drugs or devices.

The paragraphs below set out each item listed in proposed § 1271.370(a), along with the parallel regulation applicable to biological drugs or devices. The agency expects that few if any changes will need to be made to current labeling to ensure that the information listed in proposed § 1271.370(a) is provided. Where there is a difference in required placement of the information (e.g., on the label or in a package insert), the placement required in the biological drug or device regulation will apply.

a. *Name and address of the establishment that determines that the product meets release criteria and makes the product available for distribution.* For biological drugs, §§ 610.60(a)(2), 610.61(b), and 610.63 require the name, address, and license number of the manufacturer or, in the case of divided manufacturing responsibilities, all manufacturers. Section 610.64 permits the name of the distributor to appear. For human cellular and tissue-based products, FDA considers the establishment that determines that the product meets release criteria and makes the product available for distribution to be a manufacturer and will expect that manufacturer's name and address to appear on the product label.

Section 801.1(a) requires the label of a device to specify the name and place of business of the manufacturer, packer, or distributor. FDA proposes to interpret this requirement, with respect to human cellular and tissue-based products regulated as devices, as requiring the name of the

establishment that determines that the product meets release criteria and makes the product available for distribution.

b. *Description of the type of product.* For biological drugs, §§ 610.60(a)(1) and 610.61(a) require the proper name of the product to appear on the container and package label. The product's proper name will serve as an adequate description of the type of product. For devices, section 502(e)(2) and (e)(4) of the act (21 U.S.C. 352(e)(2) and (e)(4)) requires products to be labeled with their established name, or if there is no established name, then with the common or usual name of the device; either will suffice, so long as it adequately describes the type of product.

c. *Expiration date.* For biological drugs, §§ 610.60(a)(4) and 610.61(d) require products to be labeled with their expiration dates. For devices, § 801.109(c) requires products to be labeled with information on ''any relevant * * * precautions''; FDA proposes to interpret this provision as requiring a product's expiration date, if the product has one, because the expiration date is effectively a precaution against use of an out-of-date product.

d. *Storage temperature.* For biological drugs, § 610.61(h) requires the recommended storage temperature to appear on the package label. For devices, FDA proposes to interpret § 801.109(c), which requires information for use, including precautions, to include the proper storage temperature.

e. *Warnings, where appropriate.* For biological drugs, § 210.57(e) requires warnings. For devices, § 801.109(c) requires information on hazards, contraindications, side effects, and precautions, which FDA proposes to interpret as including any appropriate warnings.

f. *Instructions for use.* For biological drugs, § 610.61(i), (j), and (k), as well as § 201.57(c), requires instructions for use. For devices, instructions for use are required in § 801.109(b)(2) and (c).

IV. Inspection and Enforcement Provisions

Proposed subpart F of part 1271 contains provisions on inspections; human cellular and tissue-based products offered for import; and orders of retention, recall, destruction, and cessation of manufacturing. Subpart F of part 1271 would apply only to those establishments described in

proposed § 1271.10; i.e., those establishments that manufacture human cellular and tissue-based products regulated under the authority of section 361 of the PHS Act and proposed part 1271, but not as biological drugs or as devices. Products that the agency is regulating as devices or biological drugs will be subject to the enforcement provisions of the act and applicable regulations.

The proposed inspection and enforcement provisions are based on those contained in part 1270, subpart D, which are currently applicable to human tissue intended for transplantation. These provisions were fully discussed in the rulemaking on part 1270 (''Human Tissue Intended for Transplantation,'' interim rule (58 FR 65514 and 65517 to 65518, December 14, 1993); ''Human Tissue Intended for Transplantation,'' final rule (62 FR 40429 and 40439 to 40440, July 29, 1997).

Authority for the enforcement of section 361 of the PHS Act is provided for in part under section 368 of the PHS Act (42 U.S.C. 271). Under section 368(a) of the PHS Act, any person who violates a regulation prescribed under section 361 of the PHS Act may be punished by imprisonment for up to 1 year (42 U.S.C. 271(a)). Individuals may also be punished for violating such a regulation by a fine of up to $100,000 if death has not resulted from the violation or up to $250,000 if death has resulted (18 U.S.C. 3559, 3571(b)). Organizations may be fined up to $200,000 per violation not resulting in death and $500,000 per violation resulting in death (18 U.S.C. 3559, 3571(c)). In addition, Federal District Courts have jurisdiction to enjoin individuals and organizations from violating regulations implementing section 361 of the PHS Act.

A. Inspections (Proposed § 1271.400)

Proposed § 1271.400 addresses the inspectional process. In large part, inspections of establishments that manufacture human cellular and tissue-based products would be conducted in the same manner as inspections of firms dealing in other FDA-regulated commodities.

Establishments subject to inspection include those that perform any step in the manufacture of human cellular and tissue-based products, including recovery, donor screening, donor testing, processing, storage, labeling, packaging, and distribution. All of these establishments, including any location performing contract services, would be required to permit inspections by an authorized

FDA representative at any reasonable time and in a reasonable manner. The FDA representative would determine which areas of the establishment to inspect in order to determine compliance with the provisions of part 1271; these might include, but would not necessarily be limited to, the establishment's facilities, equipment, processes, products, procedures, labeling, and records.

Inspections would be made with or without prior notification and would ordinarily occur during regular business hours. The frequency of inspection would be at the agency's discretion.

The FDA representative would call upon the most responsible person available at the time of inspection of the establishment and could question the personnel of the establishment as the representative deems necessary. The FDA representative could review and copy any records required to be kept under part 1271, and could take photographs or make video tapes. The agency notes that, under the policy expressed in Compliance Policy Guide 7151.02, ''FDA Access to Results of Quality Assurance Program Audits and Inspections,'' the FDA representative would not ordinarily review or copy an establishment's records and reports that result from audits of the establishment's quality program established under proposed § 1271.160, when such audits are conducted according to the establishment's written quality program. This policy is intended to encourage the establishment to conduct quality program audits that are candid and meaningful. The agency would continue to have access to all information required to be maintained under proposed part 1271, such as complaint files, information on product deviations, and information on corrective actions.

At the end of the inspection, if possible violations of the regulations are found, the FDA representative would issue to the most responsible person at the establishment a list of ''Inspectional Observations'' (Form FDA–483), describing the observations of the representative that represent an observed or potential problem with the facility or with the human cellular and tissue-based products. After the report of the FDA representative is reviewed, FDA may issue additional correspondence to the establishment describing the violations to the regulations and requesting appropriate follow-up action.

The public disclosure of records containing the name or other positive identification of donors or recipients of human cellular or tissue-based products would be handled in accordance with FDA's procedures on disclosure of information as set forth in 21 CFR part 20. Under these procedures, FDA takes necessary precautions to protect the privacy of names of donors and recipients prior to public disclosure of records containing identifiers of the donor and recipients. FDA recognizes the sensitive nature of information that would identify a human tissue donor or recipient. FDA may copy records containing identification of the donors or recipients if such records are needed; for example, to document the distribution of potentially infectious human cellular and tissue-based products.

The agency invites additional comments on possible alternative inspection and enforcement provisions that would leverage agency resources, be cost-effective, and achieve the public health goals of the proposed rule. The agency welcomes comments on the advantages and disadvantages of various types of programs, such as joint agency-third party inspectional programs and joint Federal-State inspectional and enforcement programs, as well as any other alternative approach that would help ensure compliance with the proposed rule.

B. Imports (Proposed § 1271.420)

Proposed § 1271.420, which is derived from § 1270.42, is intended to clarify the administrative steps for the importation of human cellular and tissue-based products into the United States. Human cellular and tissue-based products that have been recovered from sources outside the United States can enter the country, and products that have been recovered from sources in the United States and then sent outside the United States for processing can reenter the country, consistent with the provisions of part 1271. All imported human cellular and tissue-based products would be required to be accompanied by appropriate records identifying the donor and the status of donor testing and screening in accordance with the records requirements proposed in the donor-suitability proposed rule.

As with other imports, when a human cellular or tissue-based product is offered for entry, the importer of record must notify the director of the FDA district having jurisdiction over the port of entry through which the product is imported or offered for import. ''Importer of record'' is defined in proposed § 1271.3(tt). The human cellular or tissue-based product offered for import must be held intact, under conditions necessary to maintain product function and integrity, prevent contamination, and prevent transmission of communicable disease, until it is released by FDA.

Human cellular and tissue-based products that are offered for import and found to be in violation of part 1271 would be subject to recall and destruction in accordance with § 1271.440.

C. Orders of Retention, Recall, Destruction, and Cessation of Manufacturing (Proposed § 1271.440)

Proposed § 1271.440 describes the procedures for the retention, recall, and destruction of human cellular and tissue-based products and for the cessation of manufacturing operations, and is derived in large part from § 1270.43. Section 1271.440(a) states that, upon a finding that a human cellular or tissue-based product or an establishment is in violation of the regulations in this part (and thus poses a risk of spreading a communicable disease), the agency may issue an order that the product be recalled and/or destroyed, as appropriate, or that it be retained until it is recalled by the distributor, destroyed, or disposed of as agreed by FDA, or until the safety of the product is confirmed. Alternatively, the agency may take possession of and/or destroy the violative product.

Section 1271.440(c) describes in further detail the order of retention, recall, or destruction, and describes possible alternatives to destruction. Section 1271.440(e) provides an opportunity for a hearing under 21 CFR part 16 and states that, if such a hearing is requested, any possible destruction of human cellular and tissue-based products would be held in abeyance pending resolution of the hearing request.

Proposed § 1271.440(a)(3) contains a provision not found in § 1270.43: an ''order to cease manufacturing until compliance with the regulations of this part has been achieved.'' This type of order would bar an establishment from continuing its manufacturing operations until the agency

has determined that compliance has been achieved. The order will specify the regulations at issue, and will ordinarily specify the particular operations covered by the order (e.g., distribution, labeling, etc.). Operations may not resume without prior authorization of FDA.

Authority for this new provision derives from section 361 of the PHS Act, which states that, ''[f]or purposes of carrying out and enforcing such regulations, the Surgeon General may provide for such inspection, * * * destruction * * *, and other measures, as in his judgment may be necessary.'' The agency considers these new measures to be a necessary component of its new comprehensive approach to cell and tissue regulation, which includes the proposed establishment registration and product listing and the proposed CGTP requirements.

The agency recognizes that an order to retain particular human cellular and tissue-based products suspected of being in violation of the regulations may be appropriate in some instances, and intends to continue to issue such orders as necessary. However, such a limited action against a product or products may be an inadequate enforcement tool in some instances; e.g., when an establishment fails to comply with CGTP. In that situation, it may be more appropriate to take action directly against the establishment, rather than against the products of the establishment.

For example, an order to cease operations would be appropriate in the case of an establishment that failed to establish and maintain proper procedures under proposed § 1271.260(a) for storage of human cellular and tissue-based products in such a way as to prevent their cross-contamination. Such a failure to comply with CGTP would cause potential serious communicable-disease risk from all of the establishment's products. An order to retain or destroy particular products would not prevent the establishment from continuing its faulty practices and could therefore be inadequate.

The agency expects that, typically, an order of cessation may be directed only at the distribution of human cellular or tissue-based products and would not affect the rest of an establishment's operations. However, in some cases, the order might cover a particular step in the manufacturing process. And in egregious cases involving serious CGTP deficiencies, the order might cover all of a firm's operations.

V. Proposed Revocation of Part 1270

Part 1270 contains regulations governing infectious disease testing, donor screening, recordkeeping, and enforcement for human tissue intended for transplantation. Products currently subject to the provisions in part 1270 would be considered human cellular and tissue-based products under the definition in § 1271.3(e) and would be regulated under proposed part 1271. The agency has previously announced its intention that proposed part 1271 would supersede the regulations in part 1270 (donor suitability proposed rule (64 FR 52696)). After the regulations in part 1271 go into effect, the regulations in part 1270 will be unnecessary, confusing, and duplicative. For these reasons, the agency now proposes to revoke part 1270.

VI. Proposed Effective Date

FDA proposes that any final rule that may issue based on this proposal become effective 180 days after the date of its publication in the **Federal Register**.

VII. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Analysis of Economic Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and under the Unfunded Mandates Reform Act (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Regulatory Flexibility Act requires agencies to analyze whether a rule may have a significant impact on a substantial number of small entities and, if it does, to analyze regulatory options that would minimize the impact. The Unfunded

Mandates Reform Act requires that agencies prepare a written statement under section 202 (a) of anticipated costs and benefits before proposing any rule that may result in an annual expenditure by State, local and tribal governments, in the aggregate, or by the private sector, of $100 million in any one year (adjusted annually for inflation).

The agency believes that this final rule is consistent with the principles identified in Executive Order 12866. The Office of Management and Budget (OMB) has determined that the final rule is a significant regulatory action as defined by the Executive Order and so is subject to review. Because the rule does not impose mandates on State, local, or tribal governments, or the private sector, that will result in an expenditure in any one year of $100 million or more, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act. Many of the establishments within the tissue industry would be classified as small business entities, and a number of these facilities will incur new costs. Because of the limits of information to characterize the current quality management practices at many of these facilities, and thus the increased effort required to meet the standards of CGTP, the cost impact on small business entities is uncertain. The FDA has therefore prepared an Initial Regulatory Flexibility Analysis.

A. Estimated Cost Impact

With the proposed CGTP rule, the FDA is furthering completion of the set of proposals that represent a comprehensive new system of regulating human cellular and tissue-based products. Manufacturers of tissue products may need to make certain changes to their operations to comply with the rule, such as creating new procedures and providing additional documentation. The proposed rule affects several industries involved in the manufacture of human cellular and tissue-based products. These include: Eye banks, conventional tissue banks, hematopoietic stem cell facilities, and reproductive tissue facilities.

FDA estimates are based on available administrative data on the number of facilities within each industry sector and the number accredited by various industry associations. Where good statistical data are not available, FDA's cost impact estimates have incorporated the quantified

judgments of individual experts identified through contacts with the industry associations. Because of the lack of comprehensive data to characterize patterns of current practice within each affected industry sector, and the importance of this data in development of an accurate assessment of cost impact, FDA requests detailed industry comment on the number of facilities involved in the manufacture of cellular and tissue products, and the net change in quality assurance efforts needed for those facilities to comply with the proposed rule.

1. The Number and Type of Entities Affected

The economic impact of the proposed rule is organized around four subgroups: eye banks, conventional tissue banks, stem cell facilities, and reproductive tissue facilities. The number of facilities and the percent of facilities that follow current industry standards are summarized in table 1 of this document. In estimating net new costs for facilities, it is critical to account for facility adherence to current industry standards. In a number of tissue manufacturing sectors the industry standards for many manufacturing operations meet or exceed the specifications in the proposed rule. Facilities following those standards should experience very little impact in complying with FDA-proposed standards.

As presented in table 1 of this document, FDA estimates that there are 114 eye banks currently operating in the United States, although the EBAA believes that the number of banks is declining and may currently be closer to 100. According to EBAA, virtually all operating eye banks currently comply with the industry (EBAA) medical and procedural standards for quality control. For eye banks, the costs associated with following the proposed rule result from additional quality assurance steps and process documentation as specified under the CGTP.

FDA estimates that 110 tissue banks are involved in the manufacture of other conventional tissue, e.g., pericardium, dura mater, heart valves, skin allografts, bone allografts, fascia, tendon, and ligaments (hereafter referred to as ''conventional tissue banks''). Industry sources report that approximately 75 to 80 percent of these facilities currently follow the standards for tissue banking established by the AATB. For these facilities, there will be some additional cost associated with

review of the proposed FDA rule and with alignment of their current procedures to FDA's requirements. There may also be some additional recurring cost, where documentation and quality control required under the proposed rule extend beyond current practice. For the remaining 20 to 25 percent of facilities not following the industry standard, the cost of compliance would be somewhat higher. These facilities may need to establish more formal procedures and quality control steps, and may need to devote added staff hours to performing these procedures and processing controls.

Facilities that produce stem cell products from peripheral blood or from umbilical cord blood would also be affected by the proposed rule. FDA finds that available data to estimate the number of peripheral blood stem cell (PBSC) facilities and current practices are quite limited. The actual number of PBSC facilities may range from 200 to 400. Of the estimated total involved in peripheral blood stem cell production, approximately 150 are currently accredited by the AABB and an estimated 130 have applied for accreditation by the Foundation for the Accreditation of Hematopoietic Cell Therapy (FAHCT). Industry sources estimate that approximately 80 of these facilities are seeking dual AABB/ FAHCT accreditation, indicating an unduplicated count of approximately 200 PBSC facilities assumed to be accredited by AABB and/or FAHCT. However, the manufacturing practices of non-accredited facilities are unknown. The International Bone Marrow Transplant Registry/Autologous Blood and Marrow Transplant Registry (IBMTR/ABMTR) estimates that the total number of peripheral blood or bone marrow facilities may be as high as 400[1] (i.e., 200 more than the number estimated to be accredited by AABB or FAHCT), but the

[1] Based on the National Inpatient Sample of hospital discharge data collected by the Agency for Health Care Policy Research (AHCPR) in the Health Care Utilization Project (HCUP), a total of 7,300 stem cell transplants were performed in 1994, the most recent year reported. With the number of stem cell facilities ranging from 400 to 200, this would translate to a range of 18 to 37 transplants per facility per year. Based on the implied volume of product per facility per year, a total of as many as 400 facilities would seem unlikely if the number of transplants in 1994 were representative of the current volume of demand for stem cell products.

number of IBMTR/ABMTR-estimated facilities that actually process peripheral blood (as opposed to bone marrow) is uncertain.

In addition, the proposed rule would apply to facilities involved with reproductive tissue, primarily sperm banks and Assisted Reproduction Technology (ART) facilities. For purposes of this discussion, references to ART facilities include infertility clinics, and andrology and embryology laboratories. The American Society of Reproductive Medicine (ASRM) has a membership of approximately 330 ART facilities. The ASRM also has a 1996 list of approximately 110 sperm banks operating in the United States. Based on conversations with consultants, most commercial sperm banking and most ART facilities currently adhere to industry standards similar to those in the proposed rule. The 20 largest sperm banks are estimated to handle 95 percent of the total volume of product for the industry, and these facilities are believed to follow industry standards that are comparable to the CGTP. According to industry consultants, approximately one-third of the 20 largest sperm banks are accredited by the AATB, and the remaining two-thirds are licensed by State health agencies, including the California Department of Health and the New York Department of Health. Sperm banks are also regulated under the Clinical Laboratory Improvement Amendment (CLIA) of 1988.

Andrology laboratories at ART facilities are also subject to CLIA 1988. The Committee on Laboratory Accreditation (COLA) and the Joint Commission on Accreditation of Health Care Organization (JCAHO), also inspect embryo laboratories for accreditation. The requirements for accreditation by the College of American Pathologists (CAP), which also accredits ART facilities, closely resemble those in the proposed CGTP rule, with a few exceptions. Consultants estimate that as many as 80 percent of ART facilities may currently comply with the CAP requirements.

TABLE 1.—ESTIMATED NUMBER OF FACILITIES THAT FOLLOW INDUSTRY STANDARDS

Affected Industry	Relevant Industry Standards	Percent of Firms Following Industry Standards
Eye Tissue: 100–114 facilities	EBAA[1]	100% facilities estimated compliant
Conventional Tissue: (e.g., pericardium, dura mater, heart valves, skin allograft, bone allograft) 110 facilities	AATB[2]	75–80% facilities estimated compliant

TABLE 1.—ESTIMATED NUMBER OF FACILITIES THAT FOLLOW INDUSTRY STANDARDS—Continued

Affected Industry	Relevant Industry Standards	Percent of Firms Following Industry Standards
Stem Cells Peripheral Blood (PB): 400 facilities [uncertain]	AABB or FAHCT[3]	85% accredited facilities estimated compliant
Cord Blood (CB): 25 facilities	FAHCT	100% CB facilities compliant
Reproductive Tissue Sperm Banks: 110 facilities	AATB; CAP[4] accreditation; State Licensed (e.g., NY,CA); CLIA[5]-certified	20% facilities estimated compliant (accounting for 95% of all production)
Reproductive Tissue ART[6] Facilities: 330 facilities	CAP accreditation; State licensed (e.g., NY,CA); ASRM[7] guidelines	approximately 80% facilities estimated compliant

[1] Eye Bank Association of America
[2] American Association of Tissue Banks
[3] Foundation for the Accreditation of Hematopoietic Cell Therapy
[4] College of American Pathologists
[5] Clinical Laboratory Improvement Amendments of 1988
[6] Assisted Reproductive Technology
[7] American Society for Reproductive Medicine

2. Estimated Impact on Industry Facilities

In the sections that follow, the agency considers each of the provisions of the proposed rule its estimated impact on facilities in the identified sectors of the tissue industry. The impact analysis distinguishes expected cost impacts based on both facility size and estimated current adherence with industry standards. As defined by the U.S. Small Business Administration, a small facility has revenues less that $5.0 million.

TABLE 2.—ESTIMATED COST PER FACILITY AND ESTIMATED PERCENTAGE OF FACILITIES THAT WOULD BE AFFECTED BY PROPOSED CURRENT GOOD TISSUE PRACTICES[1]

Section	Title	*Eye Banks*	*Conventional Tissue* (Small/Large)	*Stem Cell Facilities* (Compliant/ noncompliant)	*Sperm Banks*	*ART[2] Facilities* (Small/Large)
1271.150	CURRENT GOOD TISSUE PRACTICE: GENERAL	--	--	--	--	--
1271.155	EXEMPTIONS AND ALTERNATIVES	--	--	--	--	--
1271.160	ESTABLISHMENT AND MAINTENANCE OF A QUALITY PROGRAM					
(b)(2)	Functions—Procedures for sharing information	$349 (95%)	$698/ $2,004 (23%)	$0/ $698 (0%/ 80%)	$698 (5%)	$698/ $0 (5%/ 0%)
(b)(3)	Functions—Corrective actions	$414 (95%)	$828 (23%)	$0/ $828 (0%/ 80%)	$828 (5%)	$828/ $0 (5%/ 0%)
(b)(7)	Functions—Investigations	$2,022 (95%)	$2,022 (23%)	$0/ $2,022 (0%/ 80%)	$2,022 (5%)	$2,022 /$0 (5%/ 0%)
(d)(1)	Audits—Annual	$414 (95%)	$828/ $1,656 (23%)	$0/ $828 (0%/ 80%)	$828 (5%)	$828/ $1,656 (50%)
(d)(3)	Audits—Report	$138 (95%)	$276 /$552 (23%)	$207 (95%)	$207 (5%)	$207/ $414 (50%)
(e)	Computers—Validate customized software	$2,040 (10%)	$2,040 (10%)	$2,040 (10%)	$2,040 (5%)	$2,040 (5%)
(f)	Procedures—Quality program					
	—Facility with minor deficiencies	$449 (95%)	$449/ $1,159 (23%)	$449 (80%)	$449 (80%)	$449/ $1,159 (80%)
	—Facility with major deficiencies	$2,191 (5%)	$2,191/ $4,359 (5%)	$0/ $2191 (0%/ 5%)	$2,191 (5%)	$2,191/$4,359 (5%)
	—Cost for additional quality control work	$1,236 (95%)	$1,236 (23%)	$1,236 (80%)	$1,236 (80%)	$1,236 (80%)

TABLE 2.—ESTIMATED COST PER FACILITY AND ESTIMATED PERCENTAGE OF FACILITIES THAT WOULD BE AFFECTED BY PROPOSED CURRENT GOOD TISSUE PRACTICES[1]—Continued

Section	Title	*Eye Banks*	*Conventional Tissue* (Small/Large)	*Stem Cell Facilities* (Compliant/ noncompliant)	*Sperm Banks*	*ART[2] Facilities* (Small/Large)
1271.170	ORGANIZATION AND PERSONNEL					
(b)	Competent performance of functions—Sufficient personnel	– –	$15,560 (23%)	$0/ $15,560 (0%/ 95%)	$15,560 (5%)	$15,560 (5%)
(c)	Training	– –	$2,348/ $3,104 (23%)	$0/ $2,348 (0%/ 95%)	$2,348 (5%)	$2,348/ $0 (5%/ 0%))
(d)	Records—Personnel	– –	– –	– –	– –	– –
1271.180	PROCEDURES–GENERAL REQUIREMENTS	$8,280 (5%)	$8,280 (23%)	$0/ $8,280 (0%/ 95%)	$8,280 (50%)	$8,280 (50%)
1271.190	FACILITIES					
(a)	General	– –	– –	– –	$14,000 (5%)	$14,000/$28,000 (5%/ 5%)
(b)	Operation-Separation of Operations	– –	– –	$0/$14,000 (0%/ 95%)	14,000 (5%)	$14,000/$28,000 (5%/ 15%)
(b)	General-Separation	– –	– –			
(c)(3)	Facility cleaning and sanitation—Procedures	$299 (5%)	$299/ $471 (23%)	$299 (95%)	$299 (5%)	$299/ $471 (5%)
(c)(4)	Facility cleaning and sanitation—Records	– –	– –	– –	– –	– –
1271.195	ENVIRONMENTAL CONTROL AND MONITORING					
(a)	General—Procedures for ventilation and air filtration	– –	$299/ $471 (23%)	$299 (95%)	$299 (80%)	$299/ $471 (80%)
(b)	Inspections—Environmental control systems	$1,000 (5%)	– –	$1,000 (50%/ 95%)	$1,000 (20%)	$1,000/$2,000 (20%)
(c)	Records—Environmental control and monitoring activities	$162 (95%)	$162/ $324 (23%)	$162 (95%)	$162 (80%)	$162/ $324 (80%)
1271.200	EQUIPMENT					
(b)	Procedures and schedules—Cleaning, sanitizing, and maintenance	– –	$1,254/ $2,638 (23%)	$0/ $1,254 (0%/ 95%)	$1,343 (90%)	$1,343/$2,261 (90%)
(c)	Calibration of equipment	– –	$1,254/ $2,638 (23%)	$1,254 (95%)	$1,343 (5%)	$1,343/$2,261(50%)
(d)	Inspections—Routine	$204 (95%)	$408/ $816 (23%)	$204 (95%)	$204 (5%)	$204/ $408 (5%)
(e)	Records—Maintenance, cleaning, sanitizing, and calibrating activities					
	—Keeping records of cleaning and calibration activities	$162 (95%)	$324/ $648 (23%)	$162 (95%)	$162 (5%)	$162/ $324 (5%)
	—Keeping records of the use of each piece of equipment	$648 (95%)	$1,296/ $2,592 (23%)	$1,296 (95%)	$1,296 (100%)	$1,296/$2,592 (100%)
1271.210	SUPPLIES AND REAGENTS					
(a)	Receipt and verification—Procedures	$100 (95%)	$299/ $471 (23%)	$100/ $299 (95%/ 95%)	$299 (5%)	$299/ $471 (80%)
(b)	Reagents—Procedures in-house	– –	$299/ $471 (23%)	$299 (95%)		
(c)(1)	Records—Receipt of supply or reagent	$162 (95%)	$162 / $324 (23%)	$0 / $162 (0%/ 95%)	$162 (5%)	$162 / $324 (5%)
1271.220	PROCESS CONTROLS					
(b)	Processing material—Procedures for the use and removal of damaging processing materials	$299 (95%)	$299/ $471 (23%)	$299 (95%)	$299 (90%)	$299/ $471 (90%)
(d)	In-process monitoring—Procedures	$349 (95%)	$349/ $1,002 (23%)	$698 (95%)	$349 (5%)	$349/ $1,002 (5%)
1271.225	PROCESS CHANGES					

TABLE 2.—ESTIMATED COST PER FACILITY AND ESTIMATED PERCENTAGE OF FACILITIES THAT WOULD BE AFFECTED BY PROPOSED CURRENT GOOD TISSUE PRACTICES[1]—Continued

Section	Title	*Eye Banks*	*Conventional Tissue* (Small/Large)	*Stem Cell Facilities* (Compliant/ noncompliant)	*Sperm Banks*	*ART[2] Facilities* (Small/Large)
(a)	Procedures—Process changes	$698 (95%)	$698/ $2,004 (23%)	$0 /$698 (0%/ 95%)	$698 (5%)	$698/ $2,004 (90%)
(b)	Change records	$414 (95%)	$414/ $828 (95%)	$414 (95%)	$414 (90%)	$414/ $828 (90%)
1271.230	PROCESS VALIDATION					
(a)	General	$1,570 (95%)	$1,570 (95%)	$1,570 (95%)	--	--
(d)	Procedures	$1,396 (95%)	$698 / $2004 (95%)	$698/ $1,396 (95%/ 95%)		
(e)	Changes and deviations—Revalidation	$785 (95%)	$1,570 (95%)	$1,055 (95%)		
1271.250	LABELING CONTROLS–PROCEDURES	$349 (5%)	$349 / $1,002 (5%)	$349 (5%)	$349 (5%)	$349 / $1,002 (5%)
1271.260	STORAGE	--	--	--	--	--
1271.265	RECEIPT AND DISTRIBUTION					
(a)(1)	General—Document identification of product	$816 (5%)	$1,632/ $3,264 (5%)	$1,632/ $3,264 (5%)	$1,632 (5%)	$1,632/ $3,264 (5%)
(b)	Receiving activities—Procedures	--	$349/ $1,002 (23%)	$698 (95%)	$698 (5%)	$698/ $2,004 (5%)
(c)	Availability for distribution—Procedures	--	$349/ $1,002 (23%)	$349/ $698 (95%)	$698 (5%)	$698/ $2,004 (5%)
(d)	Packaging—Validation	$1,296 (95%)	$1,296 (95%)	$544 (95%)	$544 (100%)	$544 (100%)
(f)	Return to inventory—Procedures	--	$299/ $471 (23%)	$0/$399 (0%/ 95%)	$299 (5%)	$299/$471 (100%)
1271.270	RECORDS					
(a)	General	$648 (95%)	$0/ $648 (0%/ 95%)	$648 (95%)	--	--
(b)	Records management systems	$2,760 (95%)	$0/ $2,760 (0%/ 95%)	$2,760 (95%)	$2,760 (5%)	$2,760/$5,520 (50%)
(e)	Length of retention	$18 (5%)	$18 (50%/ 95%)	$18 (95%)	$18 (5%)	$18/$36 (5%)
1271.290	TRACKING					
(b)(1)	Method of product tracking-General method	$698 (5%)	$0/ $349 (0%/ 95%)	$349 (95%)	$349 (80%)	$349/ $1,002 (80%)
(e)	Recipient information	$1,632 (5%)	$0/ $3,264 (0%/ 95%)	$3,264 (95%)	--	--
(f)	Consignees	$1,380 (5%)	$1,380 (23%)	$1,380 (95%)	$1,380 (80%)	$1,380 (80%)
1271.320	COMPLAINT FILE					
(a)	Procedures	$100 (95%)	$299/ $471 (23%)	$299 (95%)	$299 (5%)	$299/ $471 (5%)
(b)	Complaint file	--	--	--	--	--
(c)	Review and evaluation of complaints	$552 (95%)	$552 / $1,104 (23%)	$552 (95%)	$552 (5%)	$552 / $1,104 (5%)
	E—ADDITIONAL REQUIREMENTS FOR ESTABLISHMENTS DESCRIBED IN 1271.10					
1271.350	REPORTING	--	--	--	--	--
1271.370	LABELING AND CLAIMS	--	--	--	--	--
	F—INSPECTION AND ENFORCEMENT OF ESTABLISHMENTS DESCRIBED IN 1271.10					
1271.400	INSPECTIONS					
(a)	Inspections—General	$708 (100%)	$708 (100%)	$708 (100%)	$708 (100%)	$708 (100%)
1271.420	HUMAN CELLULAR AND TISSUE-BASED PRODUCTS OFFERED FOR IMPORT	--	--	--	--	--

TABLE 2.—ESTIMATED COST PER FACILITY AND ESTIMATED PERCENTAGE OF FACILITIES THAT WOULD BE AFFECTED BY PROPOSED CURRENT GOOD TISSUE PRACTICES[1]—Continued

Section	Title	*Eye Banks*	*Conventional Tissue* (Small/Large)	*Stem Cell Facilities* (Compliant/ noncompliant)	*Sperm Banks*	*ART*[2] *Facilities* (Small/Large)
1271.440	ORDERS OF RETENTION, RECALL, DESTRUCTION, AND CESSATION OF MANUFACTURING	--	--	--	--	--

[1] Only sections estimated to have compliance costs for these industries are shown. No cost is estimated for a section (indicated by a double dash"--") if the background analysis (see a detailed presentation of cost assumptions provided in FDA's *Cost Impacts of the Proposed Current Good Tissue Practices Rule on Eye Banks, Conventional Tissue Banks and Stem Cell Facilities: Background Paper*, April 1999, and in *Cost Impacts of the Proposed Current Good Tissue Practice Rule on Sperm Banks and ART Facilities*, February 1999, prepared by Eastern Research Group, Inc.) shows that the requirements: (1) Do not apply, (2) have no new cost impact, or (3) are met by another section of the proposed rule.
[2] Assisted Reproductive Technology

As indicated by the information in table 2, the impact of the proposed rule varies, depending upon the sector of the tissue industry and the particular provisions of the proposed rule. For many of the proposed provisions, the facility level impact will entail development of new procedures, or revision of existing procedures. The scope and degree of complexity may vary. FDA expects that the staff typically involved in the development and finalization of facility procedures will include technicians, clerical staff, lab supervisors, and the lab director. For purposes of industry-wide estimation, the agency's analysis relies on standardized estimates of the level of effort and cost for establishing procedures. Table 3 summarizes the agency's assumptions, based on input from industry consultants.[2]

TABLE 3.—ESTIMATED LEVEL OF EFFORT AND COST PER PROCEDURE REVISED OR PREPARED TO COMPLY WITH THE PROPOSED CURRENT GOOD TISSUE PRACTICE[1]

Size Category	Minor Procedures		Major Procedures	
Small Facility	Revise Existing	Prepare New	Revise Existing	Prepare New
Staff level of effort	2.0 hrs.	6.0 hrs.	8.0 hrs.	16.0 hrs.
Cost	$99.50	$298.50	$349.0	$698.00
Large Facility				
Staff level of effort	4.0 hrs.	12.0 hrs.	27.0 hrs.	54.0 hrs.
Cost	$157.00	$471.00	$1,002.00	$2,004.00

[1] Small facilities are those with revenues less than $5.0 million. The distinction between major and minor procedures is described in the report by Eastern Research Group, Inc.

[2] A detailed presentation of level of effort and cost assumptions are provided in FDA's "Cost Impacts of the Proposed Current Good Tissue Practices Rule on Eye Banks, Conventional Tissue Banks and Stem Cell Facilities: Background Paper," April 1999, and in "Cost Impacts of the Proposed Current Good Tissue Practice Rule on Sperm Banks and ART Facilities," February 1999, prepared by Eastern Research Group, Inc. These documents will be available on the CBER website.

The analysis of impact is summarized below through a discussion of the proposed rule provisions and expected type and extent of industry impact. The pertinent section of the proposed rule is noted to facilitate reference to the related estimates in table 2.

a. *Section 1271.150—current good tissue practice: general.* The proposed rule would require manufacturers of human cellular and tissue-based products to follow CGTP. Section 1271.150(a) gives an overview of CGTP but does not present specific compliance requirements. The specific requirements are addressed in subsequent sections. Section 1271.150(b) would require that manufacturers ensure compliance on the part of contractors and proposes the establishment that should be responsible for compliance. FDA expects that facilities would use accredited referral laboratories to ensure compliance with the CGTP rule, and therefore new costs would be associated with § 1271.150(b). Section1271.150(c) explains the relationship of the proposed rule to regulations specifically applicable to biological drugs or devices and paragraph (d) defines the term ''where appropriate'' in relation to the rule. Neither § 1271.150(c) nor (d) would generate any costs for this industry because no compliance requirements are specified.

b. *Section 1271.155—exemptions and alternatives.* The proposed rule would allow establishments to request an exemption or alternative from FDA for any of the requirements of the rule. There is currently no basis for predicting industry requests for exemptions or alternatives, or for predicting the effect of these actions on compliance costs. FDA anticipates that very few facilities will consider it appropriate to be exempted from the quality standards specified in the proposed rule.

c. *Section 1271.160—establishment and maintenance of a quality program.* The proposed rule would require that facilities establish and maintain a quality program. The quality program would include: Procedures for each step in the manufacturing process, procedures for exchanging information with other establishments known to have recovered cells from the same donor, corrective action and documentation, training and education of personnel, appropriate monitoring systems, maintenance of records, investigation and documentation of all product deviations, other

actions necessary to assure compliance with the quality program; assignment of authority over the quality control program, audits, computer software validation, and other procedures specific to the quality program. A number of these functions are further specified in subsequent provisions of the rule, and the impact is estimated in the context of those provisions.

In general, FDA anticipates that almost all of the establishments in the affected industries have the appropriate facilities, equipment, and systems to support comprehensive quality management, but only those already estimated to be following industry standards are expected to have comprehensive quality programs in place. Some facilities may need to upgrade their quality program for several of the proposed requirements. These include: Procedures for sharing information, corrective actions, and investigations. Further, some facilities may need to take additional steps to administer corrective actions and conduct investigations, if they currently do so only when major deviations arise.

Although sharing of information is an industry-wide practice, some small facilities, particularly those not following current industry standards, may not have written procedures and reporting forms for this task. FDA estimates that 95 percent of industry eye banks would need to revise a major procedure; 23 percent of other conventional tissue banks, not following the current AATB standard, would need to write a major procedure to comply with this requirement; 80 percent of the peripheral blood stem cell facilities not following the FAHCT or AABB standards would need to prepare a major procedure; and 5 percent of sperm banks and 5 percent of ART facilities would need to prepare a major procedure to address this requirement.

Although FDA anticipates that most industry facilities take steps to administer corrective actions and conduct investigations, some may currently do so only when major deviations arise.

FDA estimates that 95 percent of eye banks, 23 percent of conventional tissue banks, 80 percent of stem cell facilities, and 5 percent of sperm banks and ART facilities, would need to invest additional time. The incremental time for the laboratory director to administer corrective actions and document these activities is estimated to be an additional half-hour per month of

laboratory director time at eye banks that already perform this activity to a lesser extent, and an additional hour per month at all other facilities that will be newly affected by this provision. As shown in table 2 in § 1271.160(b)(7) of the background papers prepared by FDA and Eastern Research Group Inc., (ERG) for newly required investigations in tissue facilities, FDA estimates an additional cost per year of $2,022 for an additional 2 hours per month for the laboratory director to investigate and document deviations, and an additional half hour each for the laboratory supervisor and technician to participate in the investigations.

A number of facilities would also institute other requirements of the quality program, including audits, computer software validation, and procedures specific to the quality program. Audits are part of the industry standards published by the AATB, the EBAA, by FAHCT and the AABB. However, some facilities following these standards may need to do some additional recordkeeping, and facilities not following standards would begin to conduct audits. Referring to table 2, FDA assumes that up to 95 percent of eye banks would increase their audit efforts, including additional lab director time to perform the audit and additional hours of preparation for the annual audit. An estimated 23 percent of conventional tissue banks, and an estimated 50 percent of ART facilities, would allocate additional resources for annual audits, with a higher allocation of hours at larger facilities, to prepare for, and to conduct the audit. For stem cell facilities, FDA estimates that there would be no additional auditing required at facilities following FAHCT or AABB standards, but an estimated 80 percent of facilities not following industry standards would need to spend additional time to prepare for and to conduct an audit each year. It is also assumed that approximately 5 percent of sperm banks would allocate additional staff hours for these audit-related activities.

In addition to performing the annual audit, the proposed rule would require preparation of an annual audit report. Facilities following current industry standards may need to increase the time for reporting.

FDA estimates that 95 percent of industry eye banks will experience an increase of approximately 2 hours per year of lab director time for preparing the audit report. The 2? percent of conventional tissue facilities not following AATB standards are estimated to devote 4 hours of lab director time, in the case of small facilities, and 8 additional hours of lab director time at large facilities for the preparation of an annual audit report. Laboratory directors of 95 percent of the stem cell facilities, 5 percent of sperm banks, and 33 percent of ART facilities, would spend an estimated additional 3 hours to prepare the annual audit report. Approximately 17 percent of ART facilities would also be affected, with an increase of approximately 6 hours per year of staff time for audit report preparation.

Section 1271.160 of the proposed rule further stipulates that facilities would be required to validate the computer software used in their operations. The FDA assumes that off-the-shelf commercial software packages for particular applications are already validated by the software vendor, but that a facility's custom software would require complete software validation. FDA assumes that none of the affected facilities currently validate their custom software and that approximately 10 percent of eye, conventional tissue and stem cell facilities, and approximately 5 percent of reproductive tissue facilities have developed custom software that would require full software validation under the proposed rule. While the scope of such work can vary, FDA estimates that the custom software in use has a limited scope of application, and an average of 60 hours of work by the laboratory supervisor would be required to validate custom software at a facility. Detailed presentations of these assumptions are provided in section 2.4.3 of the background reports by FDA and ERG.

The last requirement for the quality control program is for procedures that stipulate how the quality program should be operated. Industry consultants indicate that facilities have quality systems in place, but that most facilities are not aware of some minor elements that should be included in the procedures. Consequently, inspectors for accreditation groups often find a few deficiencies during initial visits. FDA estimates that about 95 percent of eye banks, 23 percent of conventional

tissue, and up to 80 percent of stem cell facilities, sperm banks and ART facilities will have minor deficiencies that would require them to revise one minor and one major procedure. In addition, FDA estimates that 5 percent of all eye banks, conventional tissue, reproductive tissue facilities, and industry non-compliant stem cell facilities, may identify major deficiencies, and would need to prepare five minor procedures and one major procedure to address those problems.

The agency further assumes that facilities may generally need to do some additional quality control work to comply with the quality control program requirements in the CGTP rule. Although some tasks would not take any additional time to perform, FDA estimates that one additional hour per month each for the laboratory director and supervisor may be needed. FDA estimates that 95 percent of all eye banks, 23 percent of conventional tissue banks and approximately 80 percent of stem cell facilities and reproductive tissue facilities would allocate this additional staff time.

d. *Section 1271.170—organization and personnel.* The proposed rule would require facilities to employ sufficient personnel with the necessary education and experience to complete their tasks. Personnel would be trained to perform their work adequately. The EBAA, AATB, FAHCT, and AABB standards for quality assurance all include provisions for appropriate personnel qualifications and training, and recordkeeping related to this requirement. It is expected that most facilities for eye banking, conventional tissue banking, and stem cell production already follow these practices as proposed. The fraction of facilities in conventional tissue and stem cell manufacturing that do not follow industry standards would incur new costs. Similarly, 5 percent of the facilities in the reproductive tissue industries would incur some new costs associated with hiring staff that meet formal training requirements. The cost of this staffing effort is estimated to be approximately $15,560 per affected facility.

FDA anticipates that the 23 percent of conventional tissue facilities, 95 percent of industry-noncompliant stem cell facilities, 5 percent of sperm banks, and 5 percent of small ART facilities would incur new training costs in complying with the proposed rule. For a small tissue establishment, these costs are estimated to average $2,348. The proposed CGTP would also require

that records of personnel qualifications and training be maintained, but because the incremental record keeping is minimal, FDA assumes that the cost to comply with this requirement would be negligible. Detailed presentations of these assumptions are provided in section 2.4.4 of the background reports by FDA and ERG.

e. *Section 1271.180—procedures: general requirements*. The proposed rule would require establishments to keep written procedures for all steps performed during manufacturing of human cellular or tissue-based products, and to perform an annual review. FDA anticipates a negligible incremental cost for most facilities following industry standards, and an additional 120 hours by the laboratory director for facilities not following the current industry standards. FDA estimates that 5 percent of eye banks would need to expand their current review efforts, and that 23 percent of conventional tissue banks, 95 percent of stem cell facilities, and 50 percent of reproductive tissue facilities would incur new costs for an annual review.

f. *Section 1271.190—facilities*. The proposed rule stipulates a number of requirements regarding the construction of facilities, covering size, location, lighting, ventilation, plumbing, drainage, and toilet and washing facilities. The facility would also be required to have properly divided areas for appropriate quality control. Cleaning requirements are also outlined, including requirements for written procedures and schedules for cleaning and documentation of cleaning activities. Based on discussions with industry experts, FDA estimates that nearly all facilities that follow industry standards would not incur new costs under the proposed CGTP rule. However, some establishments that generally adhere to cleaning standards do not have written procedures. FDA estimates that 5 percent of all eye banks, in addition to 23 percent of the conventional tissue banks, 95 percent of all stem cell facilities, and 5 percent of reproductive tissue facilities would incur the cost of writing a minor procedure for cleaning. The facilities provision of the CGTP also would require that records of cleaning be maintained. This proposed requirement is currently practiced by most facilities, and is expected to have a negligible impact on facilities not following industry standards.

g. *Section 1271.195—environmental control and monitoring*. The proposed rule would require that procedures be written for environmental control and monitoring activities or systems where an environmental condition could have an adverse effect on the human cellular or tissue-based product. The rule also would require that environmental control systems be regularly inspected and that control and monitoring activities be documented. The impact of this provision of the CGTP varies by industry sector. For eye banking, the EBAA standards already contain relevant provisions, however, some additional costs may be incurred for annual inspection of the environmental control systems and for keeping records of environmental control and monitoring activities. It is estimated that 5 percent of eye banks may incur new costs for inspection and certification of equipment. FDA anticipates that the conventional tissue facilities following AATB standards would experience no new costs, but that the remaining 23 percent of facilities would need to prepare a minor procedure to control and monitor ventilation and air filtration.

The current FAHCT and AABB standards do not provide for written procedures for environmental control and monitoring. FDA therefore estimates that 95 percent of all stem cell facilities would need to develop a minor procedure to control and monitor ventilation and air filtration to comply with the CGTP. However, because the industry standards provides for appropriate environmental controls, FDA assumes that some facilities are currently performing control activities. The agency estimates that as many as half of the facilities currently following standards may already be conducting routine inspections of their environmental control equipment. It is assumed that the remaining 50 percent of those facilities, and 95 percent of facilities assumed not to be following industry standards, would incur additional costs to inspect equipment and perform recordkeeping related to environmental control.

The agency also assumes that most reproductive tissue facilities would need to prepare written procedures, and do additional recordkeeping in compliance with the CGTP. FDA estimates that 80 percent of all sperm banks and ART facilities would incur costs to comply with this provision of the proposed rule. FDA also estimates that 20 percent of ART facilities would increase

ventilation systems inspection activities. Table 2 provides estimates of cost per facility associated with these efforts.

h. *Section 1271.200—equipment.* The proposed rule stipulates that appropriate equipment be used and any equipment used be validated. Cleaning, maintenance, and calibration of equipment would be performed according to established schedules and procedures; equipment would be regularly inspected for adherence to applicable procedures and schedules; and all such activities would be documented. In addition, facilities would be required to keep records of each use of each piece of equipment, including the identification of each human cellular or tissue-based product manufactured with that piece of equipment.

The standards related to equipment, as specified by AATB, EBAA, FAHCT, and AABB generally address maintenance procedures, and recordkeeping related to maintenance. However, the proposed rule extends beyond the industry standard for EBAA, FAHCT and AABB in the areas of equipment inspection and recordkeeping. FDA therefore estimates that 95 percent of all eye banks would allocate an additional half-hour per month for the laboratory supervisor to inspect equipment, an additional half hour per month of technician time to documenting equipment cleaning and calibration, and two additional hours of technician time per month in recording each use of the equipment.

The estimated 23 percent of conventional tissue facilities that currently do not follow AATB standards would also incur new costs related to equipment quality control. FDA estimates that small facilities would prepare one minor procedure for calibration, and for cleaning and other maintenance for each of six pieces of equipment. In addition, small facilities will allocate an additional hour per month of lab supervisor time for routine inspection of equipment, an additional hour per month of technician time for documentation of cleaning and calibration, and 4 hours per month recording each use of the equipment. FDA estimates large facilities would write minor procedures for each of eight pieces of equipment, and would allocate an additional 2 hours per month of lab supervisor time for routine inspection of equipment, an additional 2 hours per month

of technician time to record cleaning and calibration activities, and an additional 8 hours of technician time per month to record each use of each piece of equipment. It is anticipated that the facilities simultaneously preparing multiple procedures related to equipment would realize some economies of scale because of similarities across procedures. This is expected to result in a savings of 30 percent in the total amount of staff time to prepare six to eight equipment maintenance procedures at one time.

Stem cell facilities also would be expected to perform some additional work to align current practice with the proposed CGTP requirements. Current FAHCT procedures provide for routine maintenance and calibration of equipment. In addition, the AABB standards recommend that standard operating procedures (SOP's) be established for proper equipment maintenance and monitoring. To further develop procedures to address routine maintenance and recordkeeping under the proposed CGTP, FDA estimates that 95 percent of all stem cell facilities would prepare a minor procedure for calibration of each of six pieces of equipment. In addition to the preparation of procedures, lab personnel would carry out the maintenance work, estimated to require an additional half hour of supervisor time per month in routine inspection of equipment, an additional half hour per month for technicians to document cleaning and calibration work, and an added 4 hours per month of technician time to record each use of equipment. In addition, most stem cell facilities that do not currently follow FAHCT or AABB standards would incur the cost of preparing a minor procedure for cleaning, for sanitizing and for routine maintenance of six pieces of equipment.

In the reproductive tissue industry, the agency estimates that all facilities have the appropriate equipment to process the tissue products, but that only a small percentage currently conduct recordkeeping and have written procedures related to maintenance, calibration and other activities as specified under the proposed CGTP. The agency estimates that 90 percent of sperm banks and ART facilities would develop additional procedures, and that 100 percent of these facilities would need to perform additional recordkeeping related to equipment use. In addition, an estimated 5

percent of sperm banks, and 50 percent of ART facilities would devote additional resources to routine calibration of equipment. An estimated 5 percent of facilities would need to also increase efforts in routine inspection, and record keeping related to equipment cleaning and maintenance. The costs per facility associated with each of these areas of activity are presented in table 2. Section 2.4.8 of the ERG background paper provides a detailed presentation of these assumptions.

i. *Section 1271.210—supplies and reagents*. The proposed rule would require that procedures be established for receipt of supplies and reagents used in the manufacture of human cellular and tissue-based products. In particular, manufacturers would be required to verify that supplies and reagents meet specifications designed to prevent transmission of communicable disease and impairment of product function and integrity. Verification of supply or reagent quality could be accomplished with a certificate of analysis. The proposed rule would also require documentation of receipt, verification, and each use of a supply or reagent in product processing.

The existing industry standards address some or all of these activities, and the estimated impact per facility varies accordingly. EBAA standards specify that sterilized supplies and reagents should contain sterilization dates, method or appropriate expiration dates. However, the agency estimates that up to 95 percent of eye banks would be required to develop additional procedures related to receipt and verification, and would devote additional staff time to recording the receipt of supplies and reagents. Similarly, FAHCT and AABB standards contain provisions for quality control in the storage, handling and use of supplies and reagents, including maintenance of records. However, FDA expects that approximately 95 percent of stem cell facilities may be required to expand on their current SOP's and recordkeeping in order to comply with the CGTP provisions.

The current AATB standards address most of the requirements for supplies and reagents included in the proposed rule. FDA assumes that the estimated 23 percent of facilities that follow these standards would be required to prepare additional procedures for in-house reagent verification, for receipt and verification, and would devote additional staff time to keeping records of the receipt of supplies and reagents.

Based on consultant estimates that 95 percent of commercial sperm banks follow AATB guidelines, the agency estimates that only 5 percent of sperm banks and 80 percent of ART facilities would need to take new steps to comply with this proposed CGTP provision. For these facilities, the agency anticipates that each facility would need to prepare new procedures for receipt and verification of supplies and reagents, and each will devote additional staff time to recording the receipt of these materials. The estimated costs per facility are presented in table 2.

j. *Section 1271.220—process controls.* The proposed rule would require facilities to monitor manufacturing processes to ensure that specified requirements for the product are met. This includes having written procedures for the use and removal of processing material that can damage products, and procedures for in-process monitoring. The standards for tissue banking specified by the AATB include activities to address these process controls, but the EBAA, FAHCT, and AABB standards do not include specific requirements for monitoring and removal of processing material that may damage the product. FDA estimates that 95 percent of eye banks, 23 percent of conventional tissue banks, 95 percent of stem cell facilities, and 90 percent of sperm banks and ART facilities would need to prepare a minor procedure related to monitoring and removal of damaging processing material. Consultants estimate that most reproductive tissue facilities have procedures for in-process monitoring, and in these industries, an estimated 5 percent of reproductive tissue facilities would need to prepare procedures to address this activity.

k. *Section 1271.225—process changes.* The proposed regulation would require establishments to institute process change procedures that will govern modifications to established operations. Changes to processes would be documented with the date of the change, the date of implementation, the rationale for the change, and appropriate approval signatures. The current standards for AATB, FAHCT and the AABB provide for SOP's for process changes, although recordkeeping procedures are not specified. Current EBAA standards do not provide for SOP's for process changes. FDA therefore estimates that nearly all eye banks would be required to prepare a major procedure for

process changes, and would allocate an additional half hour of lab director time to document process changes.

FDA anticipates that conventional tissue banks not following the AATB standard would need to prepare a major procedure related to process changes, and nearly all tissue banks would increase related recordkeeping. The agency estimates that small conventional tissue banks would spend an additional half hour per month of lab director time to document process changes, and large facilities would allocate an additional hour of lab director time for this. FDA anticipates that almost all stem cell facilities that do not follow FAHCT or AABB standards would need to prepare a major procedure to address process changes. In addition, FDA estimates that 95 percent of all stem cell facilities would allocate an additional half hour of laboratory director time to document process changes.

According to industry contacts, most sperm banks already have established written procedures for process changes, and would therefore be in compliance with this proposed provision. FDA is also informed that ART facilities follow standards for process changes, but the procedures may not be in writing. In addition, industry consultants estimate that many reproductive tissue facilities may not keep written records of their process changes. Based on these characterizations, FDA estimates that approximately 5 percent of sperm banks and 90 percent of ART facilities would need to develop a written procedure for process changes. In addition, the agency estimates that 90 percent of sperm banks and ART facilities would need to allocate additional staff time (an estimated one half-hour per month at small facilities and one hour per month at large facilities) to record changes. The associated costs per facility are presented in table 2.

1. *Section 1271.230—process validation.* The proposed rule would require facilities to validate processes that cannot be verified through subsequent inspection and testing. Current EBAA standards do not require process validation. Although current AATB, FAHCT, and AABB standards include provisions for process validation and related recordkeeping, industry experts indicate that additional validation work would be required at nearly all facilities under the proposed rule. FDA

therefore estimates that 95 percent of all eye banks, of all conventional tissue banks and all stem cell facilities, not compliant with AABB or FAHCT, would need to prepare two major procedures related to process validation, and 95 percent of conventional tissue banks and AABB/FAHCT-compliant stem cell facilities would need to revise two major procedures. FDA estimates that 95 percent of all facilities in the tissue industry would devote additional staff time for process validation.

In addition to the initial validation work, CGTP would require revalidation of procedures. The agency estimates that 95 percent of eye banks, conventional tissue banks and stem cell facilities would need to allocate an additional amount (on the order of 20 to 40 hours) of laboratory staff time for annual revalidation.

Reproductive tissue industry consultants considered that the process validation requirement would have limited application to this industry because the tissues involved in laboratory processes (e.g., sperm and ova) are not uniform in quality. However, quality control through in-process monitoring (under § 1271.220) would be applicable to these tissues.

m. *Section 1271.250—labeling controls: procedures*. The proposed rule would require facilities to establish and maintain written procedures for controlling the labeling of products. The procedures would ensure proper identification of products and include various checks and verifications. Each product would also be accompanied by donor suitability information, if applicable. Other labeling requirements would also be met, such as labeling products appropriately with the required information.

According to consultants and industry contacts, labeling controls are usual and customary practice in the industry. FDA anticipates that only about 5 percent of all facilities in eye banking, in conventional tissue banking, in stem cell processing and in the reproductive tissue industries would need to do additional work to comply with the proposed labeling controls. FDA estimates that such facility would need to revise a major procedure for proper identification of products.

n. *Section 1271.260—storage*. The proposed rule would require that storage areas be controlled to prevent mix-ups and contamination. Temperature should be monitored and limits established, including expiration dating where appropriate. Each of the relevant industry standards contains provisions regarding storage practices. Based on agency review of current industry standards, and conversations with experts about current practices at facilities, FDA anticipates that virtually all facilities follow industry standards that would comply with this provision of the proposed CGTP. These provisions of the proposed rule are therefore expected to produce no new cost impact for facilities in eye banking, conventional tissue banking, stem cell processing, and reproductive tissue.

o. *Section 1271.265—receipt and distribution*. The proposed rule would require that procedures be established and maintained for receiving, rejecting, distributing, and disposing of human cellular or tissue-based products. Documentation of each of those activities, when performed, would also be required. Packaging and shipping containers would be validated and appropriate shipping conditions must be defined. Procedures would also be established to determine whether products returned to an establishment are suitable to be returned to inventory. Agency review of current industry standards indicates that provisions related to this area of quality control, except for package validation, are included in each of the relevant standards.

The primary impact of the proposed CGTP provisions for product receipt and distribution thus involves packaging validation for most facilities, and procedures development for facilities that do not currently follow industry standards. FDA estimates that 95 percent of eye banks, conventional tissue banks and stem cell facilities would allocate approximately 4 extra hours per month for a laboratory technician to validate packaging, particularly packaging changes. In addition, an estimated 5 percent of eye banks, conventional tissue banks, and stem cell facilities would increase lab supervisor time to document receipt of products.

The agency estimates that conventional tissue banks not following AATB standards would need to revise one major procedure for receiving products, revise one major procedure related to distribution of products, and prepare a minor procedure for return of products to inventory.

FDA estimates that 95 percent of stem cell facilities would need to write one major procedure addressing receiving activities. Facilities following FAHCT or AABB standards would also need to revise a major procedure for product distribution, while all other facilities would need to prepare a new major procedure for product distribution as well as a minor procedure for handling of products returned to inventory.

According to industry contacts, most sperm banks and ART facilities have a protocol for receiving and distributing reproductive tissue products, however, an estimated 5 percent of facilities would need to write a major procedure for receiving activities and one for distribution. Similarly, an estimated 5 percent of facilities do not currently follow industry standards for product documentation. The agency estimates that an additional 4 to 8 hours of staff time per month would be required by those facilities, for documentation activities. Industry consultants indicate that although most reproductive tissue facilities utilize ''dry shippers'' for shipped products, most do not perform formal packaging validation. FDA therefore estimates that all facilities would be required to perform packaging validation, in compliance with the proposed CGTP. Experts in the reproductive tissue industry also consider it unusual for a product to be returned to inventory; given the potential risk of product deterioration or damage. It is expected that most sperm banks already have a formal procedure for handling returned product, and that ART facilities generally have an established protocol, but not a written procedure. The agency estimates that approximately 5 percent of sperm banks and 100 percent of ART facilities therefore would be required to write a minor procedure to comply with this proposed CGTP requirement. The costs per facility for these activities are presented in table 2.

p. *Section 1271.270—records*. The proposed rule would require that records be maintained for any significant step in the manufacturing process. A records management system would need to be in place and procedures would need to be established for keeping records associated with donor suitability record keeping requirements. Records would be maintained for at least 10 years. The proposed rule would also require that records be kept of any contracts or agreements. Although

many components of the required recordkeeping system are addressed under separate provisions of the proposed CGTP, there may be a few minor gaps in the records system of a facility that would be addressed under this general provision. FDA therefore estimates that approximately 95 percent of all eye banks, conventional tissue banks, and stem cell facilities that follow FAHCT or AABB standards, would be required to write at least one minor procedure, and revise one major procedure related to recordkeeping.

The agency also estimates that additional lab director time would be allocated (estimated 40 hours at small facilities and 80 at large facilities) to set up enhanced recordkeeping where a system is already in place. System enhancement would be performed at an estimated 95 percent of eye banks, 23 percent of conventional tissue facilities, 95 percent of stem cell facilities, 5 percent of sperm banks, and 50 percent of the ART facilities.

Various industry standards specify record retention, although the time periods vary somewhat. Of those facilities following industry standards, approximately 95 percent of eye banks and the 77 percent of conventional tissue banks retain records for at least 10 years, and the remainder retain records for a minimum of 5 years. For these facilities, and the stem cell facilities that do not currently follow industry standards, FDA estimates increased record retention costs based on the cost of storing an additional 5 boxes (2.4 cubic feet each) of records per year for 5 years. The retention standards of FAHCT and AABB for records related to products are different from those concerned with facility and equipment maintenance and personnel training. All records related to the product should be retained indefinitely and records related to facility and equipment maintenance and personnel training should be retained for only 5 years.

FDA estimates that a half of the records at stem cell facilities following industry standards would need to be retained for an additional 5 years, and the annual cost will be comparable to that of other small tissue facilities. The agency also estimates that nearly all stem cell facilities that are not following industry standards will increase record retention. Almost all stem cell facilities that do not follow industry standards would be required to prepare at least one minor

procedure and to revise a major procedure related to record keeping. The laboratory director at these facilities would be expected to allocate 40 hours of time to improving the facility's current recordkeeping system.

Consultants estimate that within the reproductive tissue industries all facilities have some record management system, and many facilities have systems that meet the requirements of the proposed rule. Consultants estimate that most sperm banks and the currently accredited ART facilities have adequate records management systems in place, but that approximately 5 percent of sperm banks, and about 50 percent of the ART facilities would need to allocate additional laboratory staff time (i.e., 40 hours at small facilities and 80 hours at larger facilities) to enhance their current recordkeeping system in compliance with the proposed rule.

In addition, FDA is informed that the usual and customary practice in most ART facilities is to retain donor records for an indefinite period. Usual and customary practice in sperm banks is to retain records for at least 15 years, thus more than the 10-year period specified in the proposed rule. It is estimated that only 5 percent of sperm banks and ART facilities would need to extend record retention by an estimated 5 years. The additional cost of storing these files is based on an assumption of 5 boxes (each approximately 2 cubic feet) accumulated per year at small facilities, and 10 boxes per year at large facilities, for an additional 5 years, at a cost of 30 cents per cubic foot per year. The estimated costs per affected facility are summarized in table 2.

q. *Section 1271.290—tracking*. The proposed rule stipulates the steps needed to properly track a product from donor to recipient and vice versa. The proposed CGTP would require that facilities maintain a method for product tracking and that each product be assigned and labeled with a unique identifier. If a new identifier is assigned during the manufacturing process, procedures would be required for relating the new identifier to the old identifier. Records of product transfers would be kept in the recipient's medical records. The facility that manufactured the product would also keep track of the disposition of each product, so that the recipient of the product can be easily

identified. Facilities would be required to inform consignees of the established tracking method and would be required to document that consignees agreed to participate in their tracking method.

Product ''traceability'' is a familiar concept and common practice in eye banking, in conventional tissue banking, and in the stem cell processing industry. Eye banks following EBAA standards maintain records with information that permits tracing of product from the donor source to the patient recipient, working through the surgeon who performed the procedure. FDA anticipates that only 5 percent of eye facilities would need to enhance current tracking, and would be required to prepare one major procedure related to product tracking, spend additional staff time each month to identify and document recipient information, and would allocate additional laboratory director time to institute agreements for information sharing with the consignees who will receive products.

Conventional tissue facilities following AATB standards are able to trace all products from donation source to product recipient. Conventional tissue facilities not following AATB requirements would be required to revise a major procedure to address product tracking, allocate additional staff time each month to obtain and record information about product recipients, and allocate some additional laboratory director time (on a one-time basis) to institute formal contracts with consignees. The FAHCT and AABB standards for product tracking in stem cell facilities recommend that the facility be able to trace products to final distribution or disposition, but do not specify that formal agreements be established with consignees to assure timely tracking of products. FDA therefore estimates that 95 percent of stem cell facilities would, on a one-time basis, allocate an additional 20 hours of laboratory supervisor time to institute agreements for information sharing with the consignees who will receive products. In addition, FDA estimates that 95 percent of stem cell facilities that are not following FAHCT or AABB standards would need to revise a major procedure related to product tracking, and would need to allocate additional staff hours each month for recipient identification and documentation.

Consultants for the reproductive tissue industry indicate that although sperm banks and ART facilities generally perform product tracking and adhere to the practice of documenting recipient

information for products, current practices in assigning and documenting products with unique identifiers throughout tissue processing may widely vary, and there may be little documentation of tracking agreements with consignees. Most reproductive tissue facilities therefore would need to review current systems and perform some enhancements. It is estimated that 80 percent of reproductive tissue facilities would need to revise a major procedure related to product tracking, and would allocate additional staff hours each month for recipient identification and documentation. In addition, approximately 80 percent of facilities would need to allocate lab supervisor time to institute agreements for information sharing with the consignees who will receive products. The estimated cost per facility to perform these activities are presented in table 2.

Hospitals generally handle all categories of cellular and tissue-based products. For accreditation by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), organizations that store tissue must keep records that permit tracing of any tissue from the donor or source facility to all recipients or other final dispositions. The records must include documentation of tissue use in the patient's clinical record. Most hospitals are accredited and, therefore, are presumed to be tracking tissue to recipient. We believe that hospitals not accredited tend to be specialized facilities not handling cellular and tissue-based products. Because we know of no hospital receiving tissues and not currently tracking tissue to recipient, we expect hospitals to incur no additional costs as a result of this regulation. However, as some of our sources (Ref. 45) lack conclusive data on the adequacy of hospital recordkeeping, we welcome comment on this matter.

The proposed rule would also require that specimens of dura mater be archived for the appropriate duration under appropriate conditions to enable future testing for evidence of TSE. FDA recommends that the specimens be archived for 16 years beyond the expiration date. As CDRH guidance already recommends that such specimens be archived for 10 years, this requirement would not impose an additional tracking burden. FDA assumes the incremental cost of the longer storage time to be extremely small and the overall cost impact to be negligible.

r. *Section 1271.320—complaint file.* The proposed rule would require facilities to maintain procedures for reviewing and evaluating complaints and to maintain a file for these complaints. Facilities would be required to review and evaluate complaints and to determine whether each complaint represents an event that should be reported to FDA. Documentation of the review and evaluation would be required, even if no investigation is made. FDA finds that the AATB, FAHCT, and AABB standards explicitly address procedures or recordkeeping related to complaints. Based on discussions with industry experts, the agency assumes that nearly all facilities currently track, albeit informally, the complaints received from consignees and recipients. Facilities that would be required to prepare written procedures for handling complaints, and to review complaints on a yearly basis, would incur additional costs. The agency estimates that additional costs for facilities to maintain a complaint file would be negligible.

To fully comply with provisions in the proposed rule, FDA estimates that 95 percent of all eye banks would revise a minor procedure to include the required handling of complaints, and would allocate some additional staff time each year to review complaints. FDA assumes that conventional tissue facilities following AATB standards would already perform the necessary activities, but the estimated 23 percent of facilities not following AATB standards would need to prepare a minor procedure for complaint handling, and would allocate additional laboratory director time each year to review complaints that are received.

Although the industry standards for stem cell processing provide that records be maintained of both donor and recipient complaints, the proposed rule requires that facilities also have written procedures for complaint review. FDA therefore estimates that 95 percent of all stem cell facilities would be required to write a minor procedure to handle complaints, and that 95 percent of all facilities would also be required to allocate additional time for yearly review and handling of complaints.

Consultants assessing the impact of the proposed rule on the reproductive tissue industry estimate that about 95 percent of sperm banks and ART facilities already have written procedures

for dealing with complaints, and that 5 percent of facilities would need to prepare a minor procedure for complaint handling, and would allocate additional laboratory director time each year to review complaints that are received. The estimated costs per affected facility are presented in table 2.

s. *Section 1271.350—reporting*. The proposed rule would require facilities to review adverse reaction reports and report any adverse reactions, or product deviations, involving transmission of disease, or of the failure of a product that is fatal, life-threatening, results in permanent impairment of the body, or requires surgical intervention. Based on expert assessments of current industry practices, and the inclusion of adverse event reporting in current industry standards, the agency expects that this requirement, within the proposed CGTP framework for quality management, would impose a negligible cost on facilities in the industry.

t. *Section 1271.370—labeling and claims*. The proposed rule would require that products be labeled clearly and accurately, with information including name and address of the manufacturer, a description of the product, and product expiration date. The storage temperature, warnings, and instructions would be required on the label or on a package insert. The rule would also require that any claims on labeling be truthful and that any therapeutic claim or claim of a clinical outcome of a product would be subject to regulation under section 351 of the PHS Act and/or the act.

Industry consultants inform FDA that such elements are typically present on the labels of products manufactured by eye banks, conventional tissue banks, stem cell facilities, sperm banks and ART facilities. Proper labeling is considered very important to these industries, to prevent misuse of the product. In addition, these industries generally do not make therapeutic or related claims for their products. FDA assumes, therefore, that the industry would be in compliance with this provision of the proposed CGTP rule, and estimates that the cost impact would be negligible.

u. *Section 1271.400—inspections*. FDA could conduct inspections of any facility subject to the proposed CGTP rule. FDA would interact primarily with one responsible person for each establishment, but other personnel may also be involved in the inspection. FDA could inspect facilities, equipment, processes, products, procedures, labeling, and records, and could review and

copy any records required to be kept under the proposed rule. The agency estimates that all industry facilities would be subject to this provision of the proposed CGTP, and that inspections would occur annually. FDA estimates that up to 16 hours of laboratory technician time could be necessary, to accompany the FDA inspector through the facility and to support the inspector's information needs, and that up to 4 hours of laboratory director time would be needed for activities related to the inspection. This is expected to yield a cost of approximately $702 per facility.

v. *Section 1271.420—human cellular and tissue-based products offered for import.* The proposed rule would require importers of human cellular and tissue-based products to notify the FDA district director having jurisdiction over the port of entry through which the product is imported or offered for import. The product would be held intact until it is inspected and released by FDA.

In the cellular and tissue-based product industries there is currently very little use of imported tissue that would trigger activities for facility compliance with this provision of the proposed CGTP. FDA therefore estimates the current cost for industry compliance with this proposed requirement would be negligible.

w. *Section 1271.440—orders of retention, recall, and cessation of manufacturing.* Industry firms could incur costs to comply with orders under this proposed provision. There is little available data on which to base estimates of the future frequency and scope of tissue industry conditions and practices that would necessitate such actions on the part of FDA. The agency anticipates that product orders under this provision would be rare. FDA estimates that the yearly costs to industry resulting from such orders would therefore be negligible.

3. Summary of One-Time and Yearly Cost Impacts

The costs for each subsection of the proposed rule are the product of the estimated number of affected establishments in the industry (table 1), the establishment noncompliance rate by CGTP provision, by industry sector, and the compliance cost per establishment (table 2). Total compliance costs, summed by provision of the proposed rule, are presented by sector in tables 4 through 8.

The aggregate compliance costs for all tissue industries are summarized in table 9. The total annualized costs presented in these summary tables include the reported one-time costs, such as are incurred to prepare new procedures, annualized over 10 years using a 7 percent discount rate.

TABLE 4.—AGGREGATE COMPLIANCE COSTS FOR EYE BANKS

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs
1271.150	Current good tissue practice: general	$0	$0	$0
1271.155	Exemptions and alternatives	$0	$0	$0
1271.160	Establishment and maintenance of a quality program	$122,111	$457,459	$474,845
1271.170	Organization and personnel	$0	$0	$0
1271.180	Procedures–General requirements	$0	$47,196	$47,196
1271.190	Facilities	$1,701	$0	$242
1271.195	Environmental control and monitoring	$0	$23,245	$23,245
1271.200	Equipment	$0	$109,816	$109,816
1271.210	Supplies and reagents	$10,776	$17,545	$19,079
1271.220	Process Controls	$70,124	$0	$9,984
1271.225	Process changes	$75,593	$44,836	$55,599
1271.230	Process validation	$321,218	$85,016	$130,750
1271.250	Labelling Controls–Procedures	$1,989	$0	$283
1271.260	Storage	$0	$0	$0
1271.265	Receipt and distribution	$0	$145,008	$145,008
1271.270	Records	$369,032	$103	$52,644
1271.290	Tracking	$11,845	$9,302	$10,989
1271.320	Complaint file	$10,776	$59,782	$61,316
1271.350	Reporting	$0	$0	$0
1271.370	Labelling and claims	$0	$0	$0
1271.400	Inspections	$0	$80,712	$80,712
1271.420	Human cellular and tissue-based products offered for import	$0	$0	$0
1271.440	Orders of retention, recall, destruction, and cessation of manufacturing	$0	$0	$0
Total		$995,165	$1,080,020	$1,221,708

TABLE 5.—AGGREGATE COMPLIANCE COSTS FOR CONVENTIONAL TISSUE FACILITIES

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs
1271.150	Current good tissue practice: general	$0	$0	$0
1271.155	Exemptions and alternatives	$0	$0	$0
1271.160	Establishment and maintenance of a quality program	$77,800	$137,655	$148,732
1271.170	Organization and personnel	$393,668	$63,751	$119,801
1271.180	Procedures—General requirements	$0	$209,484	$209,484
1271.190	Facilities	$8,544	$0	$1,216
1271.195	Environmental control and monitoring	$8,544	$5,030	$6,247
1271.200	Equipment	$79,352	$62,969	$74,267
1271.210	Supplies and reagents	$17,088	$5,030	$7,463
1271.220	Process Controls	$21,128	$0	$3,008
1271.225	Process changes	$25,169	$53,096	$56,679
1271.230	Process validation	$268,024	$164,065	$202,226
1271.250	Labelling Controls—Procedures	$2,736	$0	$390
1271.260	Storage	$0	$0	$0
1271.265	Receipt and distribution	$33,713	$146,448	$151,248
1271.270	Records	$172,967	$455	$25,082
1271.290	Tracking	$47,498	$101,347	$108,110
1271.320	Complaint file	$8,544	$17,140	$18,356
1271.350	Reporting	$0	$0	$0
1271.370	Labelling and claims	$0	$0	$0
1271.400	Inspections	$0	$77,880	$77,880

TABLE 5.—AGGREGATE COMPLIANCE COSTS FOR CONVENTIONAL TISSUE FACILITIES—Continued

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs
1271.420	Human cellular and tissue-based products offered for import	$0	$0	$0
1271.440	Orders of retention, recall, destruction, and cessation of manufacturing	$0	$0	$0
Total		$1,164,775	$1,044,350	$1,210,189

Table 6.—AGGREGATE COMPLIANCE COSTS FOR STEM CELL INDUSTRIES

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs
1271.150	Current good tissue practice: general	$0	$0	$0
1271.155	Exemptions and alternatives	$0	$0	$0
1271.160	Establishment and maintenance of a quality program	$188,166	$473,119	$499,909
1271.170	Organization and personnel	$739,100	$111,530	$216,761
1271.180	Procedure–General requirements	$0	$393,300	$393,300
1271.190	Facilities	77,983	$665,000	$676,103
1271.195	Environmental control and monitoring	$77,983	$202,323	$213,426
1271.200	Equipment	$387,080	$434,198	$489,309
1271.210	Supplies and reagents	$113,430	$7,695	$23,845
1271.220	Process Controls	$260,336	$0	$37,066
1271.225	Process changes	$33,155	$108,158	$112,878
1271.230	Process validation	$625,670	$275,619	$364,700
1271.250	Labeling Controls–Procedures	$4,799	$0	$683
1271.260	Storage	$0	$0	$0
1271.265	Receipt and distribution	$446,405	$26,520	$90,078
1271.270	Records	$161,856	$2,880	$25,925
1271.290	Tracking	$377,103	$155,040	$208,731
1271.320	Complaint file	$77,983	$144,210	$155,313
1271.350	Reporting	$0	$0	$0
1271.370	Labeling and claims	$0	$0	$0
1271.400	Inspections	$0	$194,700	$194,700
1271.420	Human cellular and tissue-based products offered for import	$0	$0	$0
1271.440	Orders of retention, recall, destruction, and cessation of manufacturing	$0	$0	$0
Total		$3,571,049	$3,194,292	$3,702,727

Table 7.—AGGREGATE COMPLIANCE COSTS FOR ART[1] FACILITIES

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs
1271.150	Current good tissue practice: general	$0	$0	$0
1271.155	Exemptions and alternatives	$0	$0	$0
1271.160	Establishment and maintenance of a quality program	$272,904	$586,854	$625,709
1271.170	Organization and personnel	$256,740	$25,358	$61,912
1271.180	Procedures–General requirements	$0	$1,366,200	$1,366,200
1271.190	Facilities	$5,909	$621,600	$622,441
1271.195	Environmental control and monitoring	$94,536	$146,342	$159,802
1271.200	Equipment	$767,022	$583,549	$692,756
1271.210	Supplies and reagents	$94,536	$3,596	$17,056
1271.220	Process Controls	$115,834	$0	$16,492
1271.225	Process changes	$341,302	$165,434	$214,028
1271.230	Process validation	$0	$0	$0
1271.250	Labeling Controls-Procedures	$9,481	$0	$1,350
1271.260	Storage	$0	$0	$0
1271.265	Receipt and distribution	$335,612	$36,230	$84,014
1271.270	Records	$612,720	$400	$87,637
1271.290	Tracking	$516,010	$0	$73,468

Table 7.—AGGREGATE COMPLIANCE COSTS FOR ART[1] FACILITIES—Continued

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs
1271.320	Complaint file	$5,909	$12,254	$13,096
1271.350	Reporting	$0	$0	$0
1271.370	Labeling and claims	$0	$0	$0
1271.400	Inspections	$0	$233,640	$233,640
1271.420	Human cellular and tissue-based products offered for import	$0	$0	$0
1271.440	Orders of retention, recall, destruction, and cessation of manufacturing	$0	$0	$0
Total		$3,428,515	$3,781,457	$4,269,601

[1] Assisted Reproductive Technology

Table 8.—AGGREGATE COMPLIANCE COSTS FOR SPERM BANKS

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs
1271.150	Current good tissue practice: general	$0	$0	$0
1271.155	Exemptions and alternatives	$0	$0	$0
1271.160	Establishment and maintenance of a quality program	$12,105	$23,661	$25,384
1271.170	Organization and personnel	$15,560	$2,348	$4,563
1271.180	Procedures-General requirements	$0	$82,800	$82,800
1271.190	Facilities	$299	$28,000	$28,042
1271.195	Environmental control and monitoring	$4,776	$6,592	$7,272
1271.200	Equipment	$25,522	$26,286	$29,920
1271.210	Supplies and reagents	$299	$162	$204
1271.220	Process Controls	$5,722	$0	$815
1271.225	Process changes	$698	$7,452	$7,551
1271.230	Process validation	$0	$0	$0
1271.250	Labeling Controls-Procedures	$349	$0	$50
1271.260	Storage	$0	$0	$0
1271.265	Receipt and distribution	$12,575	$1,632	$3,422
1271.270	Records	$2,760	$18	$411
1271.290	Tracking	$27,664	$0	$3,939
1271.320	Complaint file	$299	$552	$594
1271.350	Reporting	$0	$0	$0
1271.370	Labeling and claims	$0	$0	$0
1271.400	Inspections	$0	$14,160	$14,160
1271.420	Human cellular and tissue-based products offered for import	$0	$0	$0
1271.440	Orders of retention, recall, destruction, and cessation of manufacturing	$0	$0	$0
Total		$108,628	$193,663	$209,127

TABLE 9.—SUMMARY OF AGGREGATE COMPLIANCE COSTS FOR ALL TISSUE INDUSTRIES

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs
1271.150	Current good tissue practice: general	$0	$0	$0
1271.155	Exemptions and alternatives	$0	$0	$0
1271.160	Establishment and maintenance of a quality program	$673,085	$1,678,748	$1,774,580
1271.170	Organization and personnel	$1,405,068	$202,987	$403,038
1271.180	Procedures—General requirements	$0	$2,098,980	$2,098,980
1271.190	Facilities	$94,435	$1,314,600	$1,328,046
1271.195	Environmental control and monitoring	$185,839	$383,532	$409,991
1271.200	Equipment	$1,258,976	$1,216,819	$1,396,069
1271.210	Supplies and reagents	$236,129	$34,028	$67,648
1271.220	Process Controls	$473,145	$0	$67,365
1271.225	Process changes	$475,917	$378,976	$446,735
1271.230	Process validation	$1,214,911	$524,700	$697,675

TABLE 9.—SUMMARY OF AGGREGATE COMPLIANCE COSTS FOR ALL TISSUE INDUSTRIES—Continued

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs
1271.250	Labelling Controls—Procedures	$19,354	$0	$2,756
1271.260	Storage	$0	$0	$0
1271.265	Receipt and distribution	$828,305	$355,838	$473,770
1271.270	Records	$1,319,336	$3,856	$191,700
1271.290	Tracking	980,120	265,690	405,237
1271.320	Complaint file	$103,510	$233,937	$248,675
1271.350	Reporting	$0	$0	$0
1271.370	Labelling and claims	$0	$0	$0
1271.400	Inspections	$0	$601,092	$601,092
1271.420	Human cellular and tissue-based products offered for import	$0	$0	$0
1271.440	Orders of retention, recall, destruction, and cessation of manufacturing	$0	$0	$0
Total		$9,268,130	$9,293,783	$10,613,357

B. Estimated Benefits of the Proposed Rule

The overall purpose of the CGTP rule is to prevent the introduction, transmission, or spread of communicable disease through the use of human cellular and tissue-based products. Although industry quality standards exist for most of the affected products, not all members of the industry follow these standards. FDA finds that public safety cannot be assured or effectively protected through reliance on this less formal and voluntary mechanism for quality assurance. The existing industry standards vary to some extent in their comprehensiveness. Moreover, there are variations in the extent to which the industry follows these standards.

For example, most industry consultants for the cost analysis agree that quality standards, such as those proposed by the FDA, and similar standards recommended by industry, could substantially reduce the risk of product contamination and product failure. However, most experts also opined that, because additional costs are associated with maintaining higher quality standards, and because there is no explicit patient demand for higher quality standards to prevent contamination risks, some facilities are not currently following adequate quality control standards. A regulatory requirement for quality systems would provide the incentive needed to bring all facilities to a more uniform and appropriately high standard of quality.

The primary beneficiaries of the proposed CGTP rule would be the patients who receive the cellular and tissue-based products. Benefits to patients would result from the reduced risk of

communicable disease by avoiding product contamination or product failure through CGTP. The discussion that follows considers the potential benefit of avoided problems with tissue products, based on a survey of the clinical literature.

Recent clinical literature indicates that each type of tissue product considered in the proposed rule has documented contamination or other product problems resulting from processing, or other steps in manufacturing. These reported quality problems provide a basis for assessing the magnitude of the potential benefit from further reducing events that increase the risk of communicable disease transmission. In cases involving eye tissue, conventional tissue, or stem cell products, problems have required medical intervention to treat infection, or to replace an implanted defective product. In some clinical applications, product failures have increased the risk of patient mortality. In other applications, such as embryo processing, poor product quality is associated with lower success rates (i.e., pregnancy rates) among treated patients, which results in an increase in transfer attempts. In general, FDA anticipates that the risk of communicable disease transmission from product quality problems will decline as a result of compliance with the proposed CGTP.

The sections that follow describe product-related problems associated with communicable disease transmission that are at least partly attributable to a lack of uniform quality standards in manufacturing. The costs related to correcting these problems are considered, in order to gauge the potential magnitude of the benefits associated with improved quality in manufacturing. The discussion is organized by types of tissue product.

1. Eye Tissue Products

Primary corneal graft failure is a key adverse outcome of concern following corneal tissue transplant. Such failures result in additional graft attempts. Each attempt increases the risk of communicable disease transmission by exposing the recipient to another tissue product and to another surgical procedure. Although primary corneal graft failure is relatively uncommon, its occurrence has been attributed to several factors related to tissue collection, processing and product distribution. These factors include donor characteristics such as age (Ref. 3), donor infectivity (e.g.,

with Herpes Simplex Virus) (Ref. 4) length of product storage, storage medium, and shipping distance from the eye bank to the recipient site. In a recent analysis of factors contributing to primary corneal graft failure, Wilhelmus et al. found that ''[T]he duration of donor corneal preservation may have a significant effect on endothelial vitality,'' citing studies that demonstrate endothelial cell loss in chondroitin-supplemented storage media after 7 to 10 days of storage. The authors suggest that, with modern eye bank screening and preservation procedures, a donor corneal storage time greater than 1 week increases the risk of primary failure by more than twofold.

Wilhelmus et al. include in their analysis a summary of selected findings of studies published between 1971 and 1994 reporting primary graft failure for corneal transplants using 4 °C preservation, and using a variety of preservation methods. The rates of primary graft failure ranged from 0.9 to 3.1 percent, and a combined rate of 2.1 percent was estimated across all preservation methods. In their analysis of factors associated with corneal graft failures reported to the EBAA for 1991 to 1993, the findings of Wilhelmus et al. illustrate the importance of documentation of the receipt of supplies and reagents used in tissue processing. The authors found the identical manufacturer's lot number for the preservation medium among 2 media in 34 cases, among 3 media in 36 cases, and among 4 media in 16 cases. Thus, 86 cases (approximately 59 percent of cases) with primary graft failure shared preservation media from the same lots. The lot number was unique in 45 cases (31 percent) and was not recorded in 16 cases (10 percent of cases) involving product failure. These findings also underline the importance of the proposed CGTP-required verification of quality and documentation of each particular lot of processing media used in the manufacture of a uniquely labeled and traceable product.

Primary corneal graft failure typically requires repeat surgery to replace the failed graft. According to the Agency for Health Care Policy Research (AHCPR)[3] (Ref. 5), an estimated 7,443

[3] These AHCPR estimates are based on data from the Healthcare Cost and Utilization Project (HCUP–3) National Inpatient Sample. This is a Federal-State-industry partnership to assemble health care data, based on a nationwide

corneal transplants were performed in 1994, with a mean hospital length of stay (LOS) of 2 days, and a mean total hospital charge equal to $7,530. The estimated rate of primary graft failure resulting from one or more aspects of product collection, processing, or distribution ranges from 0.1 percent (the number of cases officially reported to EBAA for the period 1991 to 1993) to as much as 2.1 percent (combined failure rate reported in the literature, across the range of preservation media currently used in eye tissue processing, cited in Wilhelmus et al.). Based on the AHCPR-reported 1994 volume of corneal transplants, the estimated cases of primary graft failure may range from 7 cases [0.001 x 7,443] to 156 cases [0.021 x 7,443]. The total cost of replacement of a failed corneal graft is estimated to include $454 of physician services, including an office visit to diagnose the graft failure prior to hospitalization[4] (Ref. 6), and initial and follow-up physician visits during patient hospitalization[5] (Ref. 6) for the repeated corneal transplant. It also includes one follow-up physician office visit to assess the outcome of the second transplant. The patient is estimated to further incur at least one week of time lost from work for the doctor visits, hospitalization and recovery of visual function after surgery. The cost of $772 for this patient time loss is estimated based on a 40-hour work week and average hourly compensation of $19.30.[6]

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inpatient sample of hospital discharge records for 1994, from 20 percent of U.S. community hospitals from 17 States. The HCUP–3 estimated hospital charges do not include physician payments.

[4] An estimated submitted charge of $76 per office visit for ophthalmology care is based on HFCA allowed payments for Medicare beneficiaries in the *Health Care Financing Review* 1997 Statistical Supplement Table 62, adjusted to estimate submitted charges.

[5] An estimated initial hospital visit charge of $214 and subsequent visit charge of $88, based on HFCA allowed payments for Medicare beneficiaries in the *Health Care Financing Review* 1997 Statistical Supplement Table 62, adjusted to estimate submitted charges.

[6] This estimate is based on the 1994 average total compensation of $36,834 adjusted by 2.9 percent annual increase between 1994 and 1997, per the *U.S. Statistical Abstract.* ($36,834 × 1,0293/2080)=$19.3

Thus, the current cost impact of corneal graft failure may range from $61,292 [7 x ($7,530+$454+$772)] to $1,365,936 [156 x ($7,530+$454+$772)].

These estimates provide an indication of the potential cost savings from avoided eye tissue product failures, based on corneal transplants. Tissue quality would improve through the institution of multiple good quality practices, including the validation of processing methods, the verification of processes quality control, and improved documentation. Since these events represent only one type of eye tissue product, the potential for benefit across all products in the eye tissue industry may be greater. The estimated benefits of CGTP applied to eye tissue, measured in terms of avoided corneal graft failures, therefore provide a lower-bound estimate of the potential benefits of the proposed rule. Based on just this one type of eye tissue product, the cost of graft failures that may be avoidable through a universal application of good tissue practices ranges from $61,292 per year, with the lower estimated failure rate, to $1,365,936 per year, based on the higher rate of primary graft failure reported in the clinical literature.

2. Conventional Tissue Products

Conventional tissue includes a wide range of products including bone allograft, skin allograft, heart valves, and other products. FDA's survey of the clinical literature indicates that bone, skin and heart valve allograft each presents a different potential for product failure and thus different kinds of benefits from improved quality assurance in product manufacture. The discussion that follows considers three distinct areas of benefit.

a. *Bone allograft products*. An analysis of the incidence, nature, and treatment of infection in bone allograft (Ref. 7) by Lord et al. demonstrates the importance of quality standards and process requirements to prevent tissue contamination. Of the 283 patients in their analysis who had received a massive allograft of bone, infection developed in 33 cases (11.7 percent). The final outcome for those 33 patients was poor compared to the 250 uninfected patients. About 82 percent (27 of the 33) of the infected allograft were considered failures of treatment because amputation or resection of the graft was required to control the infection. Potential sources of contamination

cited in the study include donor infection or contamination introduced during processing (estimated to occur in as many as 7 percent of the grafts), in addition to factors such as the duration of the operation, loss of blood, injury to soft tissue, and skin sloughing during the operation. These risk factors highlight the critical need for tissue products that are both sterile and viable.

The importance of processing validation is implied by Hardin (Ref. 8) in a review of banked bone allograft processes. In describing methods for sterilization, Hardin lists ethylene oxide as one of the most commonly used chemicals, but indicates that its effectiveness may nonetheless be questionable, because of reports of graft failures in which residues of ethylene oxide have been blamed, and some experimental evidence indicating toxicity of ethylene oxide in human tissues.

Based on an average rate of 0.057 for bone allograft failure due to contamination (based on an estimated allograft infection rate of 0.07 and an estimated 0.82 failure rate for infected bone allograft), and the assumption that all failures would be treatable through repeat surgery to replace the bone graft, the associated costs could be on the order of $33 million per year [$33,069,348= 0.057 × 39,000 × ($13,538+$1,338)]. This is based on a national estimate of 39,000 bone allograft per year[7] (Ref. 9), and an estimated $13,538 per hospitalization for repeat surgery (AHCPR HCUP–3 NIS). Physician costs per hospitalization are estimated to be $1,338 including $135 for each of two specialty physician office visits: one prior to, and one following hospitalization[8] (Ref. 6); and $1,068 for surgeon services while hospitalized, based on HCFA-reported average submitted charges per person served for orthopedic surgery[9] (Ref. 6).

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[7] *Detailed Diagnoses and Procedures, National Hospital Discharge Survey 1995*, Series 13: Data from the National Health Survey, No. 13, November 1997, table 4, p. 131.

[8] An estimated cost of $135 per service based on average submitted charges per service for ''All Other Physician'' specialty groups is used to estimate specialist office visit charges. This cost per service is reported in the *Health Care Financing Review* 1997 Statistical Supplement Table 59.

[9] See *Health Care Financing Review* 1997 Statistical Supplement Table 59, Submitted Charges, for Orthopedic Surgery.

The reported average length of stay for bone surgery is approximately 5 days. The estimated cost of patient time lost assumes that repeat surgery would require at least 1 week of time from work, at an estimated value of $772, based on a 40-hour work week and average hourly compensation of $19.30 (see footnote 6). This yields a total estimated patient time cost of $1,716,156 [0.057 × 39,000 × $772]. The total annual cost of bone allograft failure due to contamination is therefore estimated to be nearly $35 million [$34,785,504= $33,069,348+$1,716,156].

If bone allograft failures result in amputation, the direct and indirect costs would be significantly higher. For example, the cost per hospitalization for lower extremity amputation is estimated to be $24,178, based on the AHCPR HCUP–3 data. Moreover, permanent disability following amputation imposes extremely high costs on the patient, and on society.

FDA is uncertain about the extent to which the estimated cost impact will be reduced through CGTP for two reasons. First, some tissue graft failures may result from the transplant procedures rather than the bone allograft manufacture. Second, some facilities may have already developed new bone processing methods that may greatly reduce infection risk. If as much as 75 to 80 percent of the estimated risk is actually attributable to other factors, or has already been addressed through better manufacturing procedures at many facilities, the net benefit from the proposed CGTP rule applied to the remainder of bone tissue processes and facilities would be approximately $8 million [$34,785,504 × 0.23] per year.

b. *Skin allograft products*. Skin allograft represent another type of tissue product that is critically dependent on quality controls to prevent the manufacture and distribution of contaminated or defective products. The clinical literature reports cases of cytomegalovirus (CMV) transmission through skin donor infection (Ref. 10), and HIV contamination from infected donor tissue and subsequent skin tissue handling (Ref. 11). CMV infections are usually not life-threatening in healthy individuals, but present grave risks to the types of patients who typically require skin grafts. In general, patients who have suffered severe burns and require skin grafts are immunosuppressed

as a result of their injury and are therefore susceptible to potentially life-threatening CMV infections. These include pneumonitis, retinitis, gastroenteritis, hepatitis, and neurological complications (Ref. 10). Contamination of skin allograft can significantly affect burn patient survival. Because the clinical literature does not provide summary estimates of the risk of contamination of skin allografts, the agency is unable to quantify overall risk. The agency welcomes comment on the rate and severity of skin tissue contamination.

c. *Heart valve allograft*. Heart valve allograft, another conventional tissue product, provide another compelling case for process validation and quality control. Valve tissue contaminants not effectively removed in tissue processing have resulted in serious infections that, at minimum, require valve replacement and that may also result in patient death.

Sources of contamination of a valve allograft include the donor, the environment during harvesting and processing, and the operating room during implantation. Microbial contamination of valve tissue is common at tissue harvesting, with reports of over 50 percent contamination among valves retrieved in open mortuary areas. According to a study by Kuehnert et al. (Ref. 12) common contaminants found before disinfection consist of gastrointestinal and skin flora, including coliforms, viridans group streptococci, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Bacillus* species. In general, bacterial contamination can be effectively removed through standard disinfection procedures used in most tissue banks. However, tissue that remains contaminated with these pathogens, particularly *Staphylococcus* and *Streptococcus* species, can cause early onset allograft valve endocarditis. In contrast to bacterial contamination, reported rates of fungal contamination are relatively low. However, Kuehnert et al. report that rates vary widely (1.7 percent to 28.0 percent), and that the inclusion of anti-fungal drugs in the tissue disinfection regimen is not effective in eradicating fungal contamination.

Fungal endocarditis is a rare but potentially fatal complication of allograft valve replacement. According to Kuehnert et al., the incidence of fungal endocarditis following surgery for heart valve replacement with allograft is estimated to range from 0.3 percent to 1.4 percent (midpoint estimate

of 0.0085). In one reported case, the infected patient needed subsequent surgery to replace the valve and required intravenous amphotericin B for the following 8 weeks. In many cases, treatment is not successful and death results. In one review, cited by Kuehnert et al., over 40 percent of the patients who had acquired fungal endocarditis after valve allograft implantation died within 2 weeks of diagnosis.

In their study, Kuehnert et al. describe the process controls used by AATB-affiliated facilities, including the establishment, validation, and documentation of decontamination protocols. Because these regimens have not been found effective against fungal contamination, AATB-affiliated facilities routinely discard tissue with documented fungal contamination. However, according to Kuehnert et al., the supplier of over 85 percent of all heart valve allograft does not follow AATB standards, but instead follows a decontamination protocol that is reported to be proprietary. This protocol apparently includes efforts to disinfect rather than discard tissue with fungal contamination. However, efforts to eradicate fungal contamination identified in processing can be unsuccessful, and in this case, a false-negative culture following processing resulted in the tissue being distributed for patient use.

The proposed rule would require that all facilities validate the effectiveness of each step in processing, and would require that contaminated tissue that cannot be effectively disinfected be discarded or otherwise removed from processing for distribution. Based on the rates of infection and mortality risk reported by Kuehnert et al., and a total of 61,000 heart valve allografts reported per year by the National Hospital Discharge Survey (Ref. 13), there may be an estimated 519 cases per year [0.0085 × 61,000] of heart valve contamination causing fungal endocarditis. These contaminated valves may further cause an estimated 207 deaths per year [0.0085 x 0.40 x 61,000]. Changes in processing based on the proposed CGTP requirements would help to avoid these deaths. Substantial health care cost savings could also be achieved through improved processing controls. Based on an average cost of $63,096 per hospitalization for implantation of a heart valve allograft (Ref. 5), and estimated physician charges of $6,796 per case, including repeat surgery and patient

care during the average 13-day hospital stay. If the CGTP requirements avoided 80 percent of these valve infections, this might result in health care cost savings of up to $29 million [0.8 x 519 x $63,096 + $6,796)].

3. Stem Cell Products

According to the National Center for Health Statistics National Hospital Discharge Survey, approximately 8,000 stem cell transplant procedures were performed in 1994. Based on the AHCPR HCUP–3 NIS data for 1994 (Ref. 5), the average length of hospital stay for bone marrow transplant procedures was 35 days, with an average cost per stay of $168,573.

Promising outcomes from use of peripheral blood stem cells (PBSC) and cord blood-derived stem cells (CBSC) in lieu of bone marrow have resulted in increased collection and use of these products in stem cell transplants. For example, recent studies have respectively reported use of PBSC (rather than bone marrow) in 54 percent (Ref. 14) and 62 percent (Ref. 15) of cases. However, studies of stem cell products indicate that products manufactured by this industry can become contaminated during collection and processing. Moreover, the therapy-induced immunosuppression of the oncology patients who receive these products places them at particular risk for serious infection and subsequent mortality. Manufacturing methods conforming to good tissue practice are necessary to prevent this threat to the safety and effectiveness of stem cell therapies. For example, earlier investigations of PBSC reported that the large quantity of blood that must be processed to obtain adequate numbers of stem cells resulted in large volumes of cryopreserved cells received by patients. This process posed the risk of increased toxicity, because of the amount of dimethyl sulfoxide used for cryopreservation (Ref. 16).

Another quality concern with PBSC involves the maintenance of sterile integrity of the apheresis catheter and component throughout the period of leukopheresis, cryopreservation, thawing, and transfusion (Espinosa et al., 1996). Webb et al. (Ref. 14) reported a 2.41 percent rate of bacterial contamination in PBSC products, and a 13.7 percent rate of infection of patients receiving contaminated products.

Although the bacteremia-induced fever and other clinical sequelae are considered reversible, infections present more serious risks in stem cell recipients than for the general population. Survival rates for hematopoietic stem cell transplantation are significantly reduced for patients that become critically ill. In a study of survival rates among stem cell recipients admitted to an intensive care unit, Price et al. (Ref. 15) found that patients with probable infection had a significantly higher death rate (57 percent) compared to patients with no probable infection (13 percent). Multiple regression analyses by Price et al., to predict probability of death controlling for other risk factors such as patient intubation, type of transplant, source of stem cells, human leukocyte antigen compatibility, type of malignancy and patient age, also found infection to be a significant predictor of mortality.

An estimated 15 patients per year could suffer infection following receipt of contaminated PBSC, based on the reported rates of 2.4 percent of patients receiving contaminated PBSC, 13.7 percent of those patients subsequently developing infection, and 8,000 stem cell transplants reported for 1994, and assuming that 58 percent of stem cell transplants (the average of the two reported rates of PBSC transplant cited above) involve PBSC. Costs of treating patients who become infected after receiving contaminated stem cell product are based on an average AHCPR-reported hospital charge[10] (Ref. 5) of $17,981 per 9-day patient stay for treatment of bacterial infection. Estimated health care costs also include physician costs of $918 assuming one initial hospital visit, and daily follow-up visits during the patient stay[11] (Ref. 6). Patient time loss during the hospitalization is valued at $1,387, based on estimated hourly compensation of $19.30 (see footnote 4) and a 9-

[10] Based on AHCPR HCUP–3 National Inpatient Survey for 1994 hospital charges by principal diagnosis, ''bacterial infection, unspecified site'' ($17,891), *http://www.ahcpr.gov/data/94dcchpr.htm.* 1998.

[11] Physician charges are based on estimates of physician submitted charges using data reported in the Health Care Financing Review Statistical Supplement, 1997, table 62. Initial inpatient visit charge is estimated to be $214, and daily follow-up visits in the hospital are estimated to be $88 per visit. Thus total physician charges for care during the 9-day hospital stay are estimated to be $918.

day hospital stay. Thus, the total annual cost impact of patient infection following transplant of contaminated PBSC products is estimated to be $304,290 [15 x ($17,981+$918+$1,387)].

In addition to avoided health care costs, eliminating the risk of contaminated products could yield a potential of seven avoided stem cell patient deaths per year, due to infection. This number reflects the excess mortality risk reported for stem cell recipients with infection versus those without infection. It is based on the following: (8,000 transplant procedures per year) × (58 percent of procedures with PBSC) × (2.41 percent PBSC patients receiving contaminated product) × (13.7 percent patients receiving contaminated product develop infection) × (57 percent to 13 percent) excess rate of death for stem cell recipients given presence of infection.

As bacterial contamination has also been documented in a study of cord blood processing, the proposed CGTP requirements for staff training and process validation would support similar risk reduction efforts across CBSC facilities. For example, a study by Kogler et al. (Ref. 17) found that during the initial 6 months of an unrelated CB collection program, the median bacterial contamination rate was 18 percent. After extensive training in sterile procedures for the staff who collect cord blood, the contamination rate was reduced to 1 percent.

4. Reproductive Tissue Products

Most aspects of cellular and tissue product manufacturing in the reproductive tissue industry would become newly regulated under the proposed CGTP rule. The affected establishments within this industry include sperm banks and ART facilities. Reports of the sensitivity of product quality to variations in tissue collection, technician skill, processing methods, environmental conditions, and other factors (Ref. 22), indicate that the risk of communicable disease transmission would be reduced by improving the proposed overall product quality, and economic benefits would be seen through improved patient outcomes from facility compliance with the proposed CGTP requirements.

The tissue used in commercial sperm banks is washed, processed, and cryopreserved donor sperm used for therapeutic donor insemination (TDI). The sperm are obtained generally from paid donors who have been screened and tested for infectious disease and certain genetic disease risks.

The tissues used in ART facilities include fresh or cryopreserved oocytes, sperm, zygotes, and embryos. The handling of tissues include but are not limited to: Retrieval of oocytes from a female, collection of sperm from a male, in vitro fertilization (IVF), cryopreservation of fertilized oocytes not transferred in the same treatment cycle, and thawing of frozen fertilized oocytes. The success of in vitro fertilization, measured as the number of deliveries per IVF cycle, has gradually increased over the past decade or so, from 11 percent in 1985 to 18 percent in 1994 (Ref. 18). More recently, the Centers for Disease Control and Prevention (CDC) have reported average live birth pregnancy rates for ART clinics to be as high as 19.6 percent per cycle in 1995 and 22.6 percent per cycle in 1996 (Refs. 19 and 20).

Despite the increasing effectiveness of infertility treatment through ART, problems can occur in tissue processing. Adverse outcomes owing to problems with product quality can result from contamination that produces infection (e.g., HIV transmission) in the infertility patient (Ref. 21). Problems with ART facility processing of sperm or oocytes can also lead to reduced rates of fertilization, and unsuccessful IVF attempts, which would ultimately increase the number of transfer attempts. Each additional transfer attempt increases the risk of communicable disease with each attempt.

Where quality problems in tissue processing result in reduced embryo quality and lower probability of pregnancy, the patient, on average, needs to undergo more cycles of IVF to achieve a pregnancy that produces a live birth. The estimated patient cost per cycle ranges from $8,000 to $10,000 (Refs. 24 to 26).

The number of Americans who would potentially benefit from improved reproductive tissue processing is substantial. According to the 1995 National Survey of Family Growth (NSFG), (Ref. 28) 15.4 percent of American women 15 to 44 years of age, approximately 9.3 million women,

have reported receiving infertility services. Approximately 600,000 women report receiving ART's, defined in NSFG to include artificial insemination and IVF services. The number of ART procedures annually has been increasing in recent years. According to the CDC (Ref. 29) a total of over 64,000 cycles of ART were performed by U.S. facilities in 1996, compared to approximately 60,000 cycles in 1995. The proposed CGTP rule, therefore, has the potential to benefit thousands of infertile couples.

Processes that affect product quality. Recent clinical literature reports a number of factors in the manufacturing process that could affect tissue quality. These factors include technician skill, equipment accuracy and reliability, methods used in laboratory processing, and environmental controls affecting product quality. Following process validation and quality controls that would be required under the proposed rule is expected to substantially reduce or eliminate detrimental variations, and thereby improve product quality.

Sperm processing occurs in both commercial sperm banks and ART facilities. Commercial sperm banks generally screen, wash, and cryopreserve donor sperm. ART facilities typically include an andrology laboratory that performs semen analysis and conducts IVF. Variations in methods and technician skills at various stages of sperm processing have been associated with variations in quality. Poor sperm quality increases the probability that additional tissue transfer procedures will be necessary. For example, in a study conducted to establish quality controls in semen analysis, Yeung et al. found that the subjective thresholds for judging sperm motility (a key measure of sperm function for diagnosis and treatment) differed for each technician performing the analysis (Ref. 30). The establishment of values for threshold velocities, and standards for technician training were identified as methods to improve consistency in technician assessments.

A study by Mahmoud et al. (Ref. 31) compared 10 different methods for estimation of sperm concentration (another key indicator of sperm quality) and reported substantial differences in the accuracy of laboratory assessments, depending upon the type of pipette and the method used. They found that although a few devices and methods produced accurate, low-variability estimates, others

had a tendency to overestimate or to underestimate sperm concentration. These findings strongly support the need for equipment calibration and laboratory method validation.

In addition to processing steps related to the sperm quantity and quality, sperm processing for IVF typically requires that sperm be purified, removing semen fluid, cellular debris, white blood cells, and other contaminants that may interfere with fertilization. Many sperm separation methods have been developed and are in use in ART programs, including basic sperm washing, swim-down and swim-up techniques, refrigeration/heparin techniques, separation with Sephadex and Ficoll columns, separation with glass wool and Percoll gradient centrifugation (Refs. 32 to 34). No single method has become the standard, although some approaches may be more effective than others in preserving functional integrity. For example, when King et al. (Ref. 35) compared the effect of different antibiotics used in sperm washing, they found that some agents produced severe adverse effects on sperm motility and actually decreased sperm fertilizing capacity. The importance of product quality in this step of processing offers another example of the value of process validation in ensuring sperm product viability and thus successful fertility treatment for patients.

Environmental controls present another area with a demonstrated need for quality control in reproductive tissue processing. Environmental contamination may come from many sources, including the air, water or laboratory supplies. A study of laboratory air quality in ART facilities by Cohen et al. (Ref. 36) found that over 300 volatile organic compounds were detectable in spite of the use of centralized high efficiency particulate air (HEPA) filtration, generic but centralized carbon and pre-filtration, and numerous ionization units placed at strategic points in the laboratory. Potential sources of contaminants included vehicle and industrial emissions in outside air, use of plastics and disposable plasticware in the laboratory, equipment (e.g., freon leakage from refrigeration units), cleaning agents and equipment lubricants, and air flows from activities in adjacent areas of the building.

A more detailed study of these factors by Cohen et al. was prompted in part by the sudden and significant declines in clinical pregnancy and implantation rates that occurred at two points in time at an ART facility. In those instances, the pregnancy rate had declined by about 50 percent and subsequent implantation rates also declined. Their investigation revealed that, in the first instance of decline, a fumigation with pesticides had taken place in areas of the building adjacent to the ART facility, without notification given to the ART facility. The second episode of sudden decline corresponded to the installation of a redesigned air filter in the facility. Further air sampling also revealed that chemical contaminants produced in another area of the building, which was used as an outpatient surgery center and was not part of the ART clinic, could be detected in the embryo laboratory when more sensitive monitoring equipment was used. Cohen et al. proposed various measures to counter these potential sources of chemical air contamination in both the laboratory and the embryo incubators. Laboratories without adequate environmental monitoring and controls would not be able to detect such degradations in air quality.

An earlier study of mouse embryos by Francis et al. reported that some brands of nonpowdered surgical gloves appear to be embryotoxic (Ref. 37). Temperature fluctuations during cell culture, and to a lesser extent, the time between retrieval and transfer, may also affect tissue quality and thus increase the probability of additional transfer attempts (Ref. 39).

The lack of experience and training of laboratory personnel also could increase the need for additional transfer attempts due to poor tissue quality. One study found that new embryologists needed several months to gain the experience to consistently predict nuclear maturity from cumulus-coronal morphology. Moreover, even when a stable prediction rate was reached, it rarely exceeded 72 percent accuracy (Ref. 40). Yet consistent assessments of product quality and transfer of high quality embryos to the patient are critical to increasing the overall success of IVF treatment and to minimizing transfer attempts.

Although there has been some Federal and some private sector standard setting and oversight in the reproductive tissue industry, existing standards do not provide the level of quality

management and process quality assurance that would be required under the proposed CGTP rule for all tissue establishments. A voluntary accreditation program jointly offered by the CAP and the ASRM has been available to ART laboratories since 1992 (Refs. 41 and 42), and the number of facilities seeking accreditation has been increasing in recent years. The problems with product processing cited in recent clinical literature, however, suggest that although there is increasing interest in quality assurance, there are still substantial gains that could be made in tissue facilities, by implementing the proposed CGTP rule.

In addition to the benefits that would accrue directly from implementation of this proposed rule, individuals may reap ancillary benefits that could arise indirectly from the rule. Although the proposed rule would provide a direct benefit from the decreased risk of communicable disease transmission, the public, particularly couples seeking assistance in beginning a pregnancy, could receive an indirect economic benefit. Such ancillary economic benefit, although not certain, would be seen as an increase in ART facility success rates and a decrease in health costs associated with a reduction in the number of IVF attempts per live birth.

FDA cannot predict the precise impact from implementation of the proposed CGTP rule. To obtain an estimate of benefits and to capture a level of uncertainty, this analysis considers three potential scenarios and presents the results a range of possible outcomes. In general, it is assumed that the rule will affect the facilities with the lowest success rates and that these facilities would improve to some minimal level of performance from the implementation of good practices. In one scenario, benefits are assumed to be limited to the worst-performing quarter of all facilities. These facilities would improve to the level of the facility just better than the bottom one-fourth. In another scenario, the half of all facilities with the lowest success rates would improve to where they would be as good as the median facility. In a third scenario, implementation of the rule would not change ART facility success rates.

The scenarios consider only the cycles of treatment for younger women (age less than 35) for whom patient age is not likely to be a confounding factor affecting oocyte quality. Of the

22,811 fresh nondonor cycles of treatment for these patients at the 300 ART facilities reporting data for 1996, the average success rate was 28.65 live births per 100 cycles, and the median live birth pregnancy rate was 26.3 percent per cycle.

Scenario 1 assumes that the facilities currently achieving the lowest success rates (i.e., the lowest quartile of success rates reported for ART establishments) are able to increase their average success rate to the rate corresponding to the 25th percentile rate. This would represent a first step and as technology and techniques continue to improve, so would success rates. In the 1996 report, the 25th percentile rate was 19.7 live births per 100 cycles. FDA finds that raising the bottom quartile of 75 facilities, to 19.7 live births per 100 cycles, would reduce the IVF attempts from a reported 4,756 to an estimated 3,591 treatment cycles. This improvement would decrease transfer attempts and yield an estimated savings of $10.5 million for patients and other payers, based on an estimated average cost of $9,000 per cycle, and an estimated 1,165 avoided cycles [4,756 - 3,591].

Scenario 2 assumes that facilities in the lower half of the industry distribution are able to bring their success rates up to the median rate of 26.3 live births per 100 cycles. The increased success rate is assumed to be achieved through improvement in staff training and skill, processing validation, and quality control throughout the facility in accordance with the proposed CGTP rule. Under this scenario, the affected 150 facilities would reduce the number of IVF attempts from a reported 10,414 cycles to an estimated 7,662 treatment cycles, to achieve the same number of successful treatments. This would yield an estimated cost savings of $24.8 million for patients and other payers. This is based on an estimated 2,752 avoided cycles of treatment [10,414 - 7,662] and assumed average cost of $9,000 per cycle of IVF treatment.

At the other end of the spectrum, Scenario 3 provides for the possibility that this proposed rule would have no effect on success rates at ART facilities or the number of IVF attempts per live birth. In such a case, there would be no additional economic benefit beyond the benefits previously discussed, including an anticipated decrease in communicable disease transmission.

Couples seeking infertility care incur an indirect cost of time lost (e.g., work time) while undergoing treatment. Using an average hourly wage of $19.30[12] and assuming 6 hours of time (e.g., 4 hours for the female and 2 hours for the male patient) per couple per cycle of IVF treatment, the estimated value of the lost time would be as follows. Under Scenario 1, the estimated 1,665 avoided treatment cycles would yield a time gain valued at $192,807 [1,665 × $19.30 × 6]. Under Scenario 2, the 2,752 potentially avoided treatment cycles would yield a time gain valued at $318,682 [2,752 × $19.30 × 6]. Under Scenario 3, there would be no avoided treatment cycles and, thus, no quantifiable benefits.

C. Summary of Potential Benefits Resulting From Avoided Quality Problems in Processing of Cellular and Tissue Based Products

This analysis of benefits of the proposed CGTP rule has considered its impact on major sectors of the tissue industry by focusing on product quality problems cited in the literature. This review suggests that industry standards are not applied uniformly resulting in uneven product quality.

Table 10 provides a summary of the particular products and problems identified in the agency's survey of literature. FDA estimated the potential benefits of avoiding quality problems based on reported risks and national data-based estimates of the number of patients undergoing related procedures. Depending on the particular industry sector, the potential quantified benefits from reduced health care costs are estimated to range from approximately $61,000 per year, to approximately $33.5 million per year. The total estimated potential quantified benefits range from a total of $41.9 million to $68.0 million. The actual level of benefits that would be realized through wide application of CGTP is uncertain, however, as the agency's projections are sensitive to numerous assumptions that appear plausible, but remain to be tested.

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[12] Estimated hourly compensation of $19.30 is based on the 1994 average total compensation of $36,834, adjusted by 2.9 percent annual increase reported in the 1997 *U.S. Statistical Abstract.*

TABLE 10.—SUMMARY OF POTENTIAL BENEFITS OF PROPOSED CURRENT GOOD TISSUE PRACTICE BASED ON TISSUE PROBLEMS CITED IN REVIEWED LITERATURE

Tissue Industry Sector	Tissue(s) Considered	Avoided Problems with Tissue	Avoided Treatment or Outcome	Potential Cost Savings/ Year
Eye Tissue	corneal graft	graft failure	repeat surgery; increased graft attempts	$61,000 to $1.4 million
Conventional Tissue	bone allograft	bone infection; graft failure	repeat surgery/amputation; increased graft attempts	$8 million
Conventional Tissue	heart valve allograft	fungal endocarditis	repeat surgery/patient death; increased transplant attempts	$29.6 million 176 excess deaths
Peripheral Blood and Cord Blood Stem Cells	stem cell transplant	infection in cancer patients	hospitalization/patient death	$304,000 7 excess deaths
Reproductive Tissue	sperm, oocytes, zygotes, embryos	IVF[1] failure	additional IVF treatment cycles	$0 to 24.8 million
Total Potential Cost Savings/Year				$41.9 to $68.0 million

[1] In vitro fertilization

Uncertainties affecting the true level of benefit include: The actual extent of current CGTP compliance in each of the affected industries, the lack of more complete information about the incidence and severity of problems from processing of tissue products, the net impact of those quality problems on patient outcomes, and the size of the affected patient population. Because of the limits of available data, the foregoing analysis has focused on a limited set of tissue products. It is not certain how well these data represent the most critical areas or actual scale of risks in the tissue industry. For some products, such as demineralized bone, the industry has achieved important advances in processing that have improved the safety and effectiveness of its products. Thus, the analysis of benefits based on problem reports from several years ago may overstate the potential for improvements in the current best industry practice. In other cases, the publication of the recent problem reports suggests that deficiencies still exist within current practices. These areas present important opportunities to avoid unnecessary patient risks and health care costs.

D. Small Entity Impacts

The Regulatory Flexibility Act (RFA) requires agencies to determine whether a proposed rule may have a significant effect on a substantial number of small entities. Tissue and blood banks are classified in North American Industry Classification System (NAICS) 621991. In this industry category, any firm with annual revenues less than $5.0 million is considered small by the U.S. Small Business Administration. In every sector of the cell and tissue product industry, the majority

of establishments are estimated to be classified as small entities. However, because of the high level of current compliance with industry standards, the increase in costs is expected to be limited primarily to facilities that do not comply with industry standards. To measure the impact of CGTP on small businesses, FDA calculated the ratio of industry compliance costs to industry revenues, assuming that all facilities incurred the same cost. The small entity impacts estimated below focus on the facilities that will be newly compliant under the proposed CGTP, and thus will experience the highest potential new costs. In addition, although current quality management practices at non-accredited or less-than-fully compliant facilities may vary, and not every facility will incur every new cost estimated in table 2, the analysis that follows considers a high-cost scenario where every estimated cost is incurred, in order to produce a conservative estimate of the potential impact on small entities. While some firms may have lower than average revenues, making them potentially more sensitive to cost increases, FDA does not know the distribution of firms by revenues. FDA welcomes comments on this issue.

Within the eye banking industry, experts estimate that virtually all facilities would be classified as small, and believe all are to be compliant with the industry EBAA standards. The average annual revenue per eye bank is estimated at $1.2 million (Ref. 44). If an eye bank were to incur every new cost estimated for facilities in that industry, the total cost impact, including total one-time costs and the yearly cost, would be $36,738, which represents an estimated 3 percent (0.03) of estimated annual revenues. Average annualized compliance costs per eye bank are estimated to be $10,717, or 0.89 percent of annual revenue per firm.

In the conventional tissue industry, an estimated 75 to 80 percent of the total of 110 facilities would be classified as small entities. Industry experts also estimate that 75 to 80 percent of those facilities currently comply with the AATB standards, which generally meet or exceed the requirements of the proposed CGTP rule. Based on the assumed levels of increased effort and costs shown in table 2, the remaining 23 percent of small facilities that do not comply with AATB standards would incur up to $62,662 in total new costs, including both the total one-time cost

and the yearly cost, assuming that every potential area of new quality management effort would be needed at every one of these facilities. The average annual revenue per small conventional tissue bank is estimated at $1.2 million (Ref. 44). The estimated total new costs would represent approximately 5 percent of this annual revenue figure. The average annualized compliance cost for a small conventional tissue bank is estimated to be $10,310, representing 0.86 percent of firm revenues.

The agency anticipates that all stem cell facilities would be classified as small entities, and estimates that these establishments have annual revenue averaging $1.2 million (Ref. 44). Establishments that comply with the current FAHCT or AABB standards would incur some additional costs. If each of these facilities were to incur new costs for every provision identified in table 2, the total cost per facility, including total one-time and yearly costs, would be approximately $20,270. This figure represents approximately 2 percent of estimated annual revenues. Stem cell facilities that do not currently comply with AABB or FAHCT standards would incur greater costs, as shown in table 2. If each of these facilities were assumed to incur every new cost identified in the cost analysis, the total one-time cost plus annual cost would be approximately $79,337. This figure is equal to approximately 7 percent of estimated annual revenues. The average annualized compliance costs incurred by stem cell facilities would similarly vary depending on current facility practices and compliance with AABB or FAHCT standards. If a facility is currently compliant with these industry standards, the average annualized cost of compliance with the proposed rule is estimated to be about $7,407, representing 0.62 percent of the yearly revenue of these firms. However, if a facility is not currently compliant with the requirements of the current industry standards, a greater level of new effort would be required for quality assurance and quality management. The average annualized cost per facility is estimated to be $40,721, which would represent 3.39 percent of an average annual revenue of $1.2 million.

Consultants estimate that approximately two-thirds of all ART facilities (approximately 200) would be classified as small entities, and have average annual revenues of $2.5 million. Based

on the project levels of compliance with various provisions of CGTP, as described in the cost analysis, if a facility were to incur every potential new cost, as shown in table 2, the total one-time plus annual cost to the facility would be $83,302. This total would represent approximately 3 percent of average annual revenues. The average annualized compliance cost per facility is estimated to be $11,342, representing approximately 0.45 percent of annual revenues.

According to recent estimates by a sperm banking industry expert, approximately 100,000 TDI units are produced each year from collected and processed sperm donations. An estimated 95 percent of that total production is handled by the largest 20 facilities. Nineteen of the largest 20 facilities are estimated to have average annual revenues of approximately $2 million, and only 1 of the 20 is estimated to have revenues greater than $5 million per year. The remaining 5 percent of industry production, or 5,000 TDI units, are processed by very small banks described by an industry expert as typically functioning within a physician office practice (e.g., that of an obstetrician (ob) or a gynecologist (gyn)). The sperm banking in these facilities is generally offered as an additional service to patients receiving fertility treatment, and is not the primary line of business of these establishments. The annual revenue for these individual physician practices is estimated to be $252,000 per year, based on the mean physician income of $215,000 after expenses and before taxes for the ob/gyn specialty category, reported in the 1992 American Medical Association (AMA) survey (Ref. 45), adjusted to 1998 assuming an average annual wage inflation of 2.7 percent, based on yearly rates reported by the Bureau of Labor Statistics. Thus the majority of sperm banks would be considered small entities.

If each of the small sperm banks were to incur every potential new cost of compliance with the proposed CGTP rule, as shown in table 2, the total one-time cost plus annual cost would equal $83,302, which would be approximately 4 percent of the $2 million in annual revenues for the ''larger'' small facilities. The average annualized cost to these banks is estimated to be $11,007, representing approximately 0.55 percent of annual revenues. Although these cost figures would account for a much larger percentage of individual physician practice income, the sperm

banking provided by these establishments is considered to represent a small and generally nonessential part of their business. For the smallest banks, the estimated 5,000 TDI units supplied by the estimated 90 facilities translates to an average volume of 55 units per facility per year. With an estimated price of $95 to $145 per TDI unit (Ref. 46) and an estimated profit of 15 percent, the banks would realize a net income of $12.40 to $19.00 per unit, or average net income of $682 to $1,045 for 55 units. This income would represent only 0.3 percent (0.0027) to 0.4 percent (0.0041) of the estimated $252,000 in annual net income for the ob/gyn physician practice. Thus, it seems likely that physician practices that currently operate small-scale sperm banking may prefer to discontinue banking, and refer their patients to a commercial bank for this service.

In summary, the majority of facilities within each sector of the tissue industry are expected to qualify as small entities. The actual cost impact on each facility is uncertain because of the limited information available to describe the current practices and compliance with industry standards at each of these facilities and within each distinct industry sector. Based on the limited available data and expert opinions, the agency estimates impacts that would result in an average annualized cost per facility ranging from $ 7,000 to $11,000 for facilities that currently comply with an industry standard, to over $40,000 in average annualized costs for facilities that do not currently comply with most industry quality standards. These annualized costs represent 0.45 to 3.39 percent of the estimated total average annual revenues.

The agency is uncertain about the accuracy of these estimates, however, because of the lack of good data on revenues for these facilities. Because of the importance of this information in accurately assessing the impact on small entities, the agency requests that industry provide detailed comment on the percentage of facilities that qualify as small entities in the eye tissue, conventional tissue, stem cell, and reproductive tissue industries; the percentage of those facilities that fully comply with current industry standards; and the specific areas where industry anticipates substantial differences between current manufacturing practices and the quality assurance elements specified

under the proposed rule. For those areas of identified difference, the agency further requests estimates of the resources and costs that will be required for facility compliance.

Although the proposed rule would impose some costs on small entities involved in the manufacture of cellular and tissue-based products, the agency believes that the proposed approach represents an effective means of protecting patient safety and public health in the manufacture of human cellular and tissue-based products. The less burdensome alternative to the proposed approach, i.e., continue with the use of trade organizational standards by industry, involve fewer requirements for small entities (the vast majority of facilities in this industry), but fail to provide fundamental aspects of product safety. Reliance on trade organization voluntary standards for good tissue practice, rather than establishing a regulatory requirement, would not ensure uniform or consistent compliance and would preclude the agency's ability to effectively monitor tissue products to ensure public health and safety. While each trade organization varies in their standards or guidelines, regulatory requirements for good tissue practice would help ensure consistency among manufacturers. FDA finds that this proposed rulemaking would enhance both public health and public confidence in the safety and quality of cellular and tissue-based products, while imposing only a minimum burden on the affected industry sectors.

IX. References

The following references have been placed on display in hte Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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X. The Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 350193520). A description of these provisions is shown below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing the instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Reporting and Recordkeeping Requirements in Current Good Tissue Practice.

Description: Under the authority of section 361 of the PHS Act, FDA is proposing new regulations to require manufacturers of human cellular and tissue-based products to follow CGTP, which would include information collection provisions such as the establishment and maintenance of SOP's, recordkeeping, reporting, and labeling of the products. The CGTP information collection provisions would provide: (1) additional measures for preventing the introduction, transmission, or spread of communicable diseases; (2) step-by-step consistency in the manufacturing of the product; (3) necessary information to FDA for the purpose of protecting public health and safety; (4) accountability in the manufacturing of cellular and tissue-based products; (5) information for meaningful FDA inspections; (6) information facilitating the tracking of a product back to its original source or to a recipient; (7) information to FDA of any adverse reaction; and (8) information that would aid in the investigation of any introduction, transmission, or spread of a communicable disease.

Table 11 lists provisions that would require reporting or disclosure of information to third parties, the Federal government, or the public. Section 1271.155(a) would require the submission of a request for FDA approval of an exemption or an alternative from any requirement in subpart C or D of part 1271 of the proposed rule. When documentation on the determination of donor suitability is translated into English, § 1271.270(c) would require a statement of authenticity by the translator. Section 1271.290(c) would require a unique identifier be affixed to each cellular or tissue-based product to relate the product to the donor and all records pertaining to the product. Whenever an establishment initially distributes product to a consignee, § 1271.290(f) would require the establishment to inform the consignee, in writing, of the product tracking requirements and the methods the establishment uses to fulfill the requirements. Establishments described in proposed § 1271.10 would be required under proposed § 1271.350(a) and (b) to report to the agency any adverse reaction or any error or accident that may reasonably be expected to lead to a reportable

adverse reaction as defined in proposed § 1271.3(ee). Section 1271.370(a)(2) and (a)(3) would require establishments to include specific information on the product label and package insert.

Table 12 lists recordkeeping provisions under the proposed rule, establishments would be required to prepare and maintain written SOP's for all significant steps performed in the manufacturing and tracking of human cellular and tissue-based products. As calculated in table 12, the preparation of the SOP's would result in a one-time impact on establishments rather than the year to year maintenance of the SOP's because, once composed, SOP's would only be reviewed annually and updated as necessary.

The SOP provisions proposed under part 1271 in the combined maintenance estimate include: (1) § 1271.160(b)(2) (receiving, investigation, evaluating, and documenting information received from other sources); (2) § 1271.160(f) (quality program); (3) § 1271.180 (all significant steps performed in the manufacture of human cellular and tissue-based products); (4) § 1271.190(c)(3) (facility cleaning and sanitization); (5) § 1271.195(a) (control and monitoring of environmental conditions); (6) § 1271.200(b) (cleaning, sanitizing, and maintenance of equipment); (7) § 1271.200(c) (calibration of equipment); (8) § 1271.210(a) (receipt and verification of supplies and reagents); (9) § 1271.210(b) (validation and/or verification of in-house reagents); (10) § 1271.220(b) (use and removal of processing material); (11) § 1271.220(d) (control of in-process product); (12) § 1271.225(a) (verification or validation of changes to a process); (13) § 1271.230(d) (maintenance and control of validated processes); (14) § 1271.250 (labeling of human cellular and tissue-based products); (15) § 1271.265(a) to (c) (receipt, acceptance or rejection, distribution, and destruction or other disposition of human cellular or tissue-based products); (16) § 1271.265(f) (suitable for return to inventory); (17) § 1271.270(b) (records management system); (18) § 1271.290(b) (method of product tracking); and, (19) § 1271.320(a) (review, evaluation, and documentation of all complaints).

Proposed part 1271 would require the following additional recordkeeping provisions listed under table 12. Section 1271.155(f) would require an establishment operating under the terms of

an exemption or alternative to maintain documentation of the terms and date of FDA approval. Section 1271.160(b)(3) would require documentation of corrective actions taken as a result of an audit of the quality program. Section 1271.160(b)(7) would require documentation of all product deviations in manufacturing cellular or tissue-based products. Section 1271.160(d)(3) would require documentation of the results of all audits and reaudits of the quality program. Section 1271.160(e) would require documentation of computer validation activities and results when computers are used as part of the quality program, as part of manufacturing, or for maintaining data or records. Section 1271.170(d) would require the maintenance of records of education, experience, training, and retraining of all personnel. Section 1271.190(c)(4) would require documentation of all significant facility cleaning and sanitation. Section 1271.195(c) would require documentation of environmental control and monitoring activities. Section 1271.200(e) would require documentation of all equipment maintenance, cleaning, sanitizing, calibration, and other activities. Section 1271.210(c) would require documentation of the receipt, verification, and use of each supply or reagent. Section 1271.220(b) and (d) would require documentation of the adequate removal of processing material and the verification activities for in-process product. Section 1271.225(b) would require documentation of all changes to established processes, including rationale and the date of implementation. Section 1271.230(a) would require documentation of validation activities when the results of a process cannot be fully verified by subsequent inspection and tests. Section 1271.230(b) would require documentation of the validation of any process-related claim. Section 1271.230(e) would require documentation of the review and evaluation of a process and revalidation of the process, if necessary, when any changes to or deviations from a validated process occur. Section 1271.260(b)(3) and (d) would require documentation of the storage temperature of human cellular and tissue-based products and any corrective action taken when acceptable storage conditions are not met. Section 1271.265(a) and (b) would require documentation of the receipt, acceptance or rejection, distribution, and destruction or other disposition of a human cellular or tissue-based product. Section 1271.270(a) and (c) would require documentation of each significant

step in manufacturing required in subparts C and D of part 1271, the results and interpretation of all testing and screening for relevant communicable disease agents and diseases, and the determination of donor suitability.

Section 1271.180 would require the retention of obsolete procedures for 10 years. Section 1271.270(e) would require the retention of all records for a period of 10 years after their creation. Records pertaining to a particular human cellular or tissue-based product would be required to be retained at least 10 years after the date of implantation, transplantation, infusion, or transfer of the product. If the date of implantation, transplantation, infusion, or transfer is not known, then records would be required to be retained at least 10 years after the date of the product's distribution, disposition, or expiration, whichever is latest. This retention time is necessary because certain cellular and tissue-based products have long storage periods. In addition, advances in medical technology have created opportunities for diagnosis and therapy for up to 10 years after recipient exposure to a donor later determined to be at risk for communicable disease agents or diseases.

Section 1271.270(f) would require documentation of any contract, agreement, or other arrangement with another establishment under which any step in the manufacturing process is performed by the other establishment. Section 1271.290(e) would require documentation of the disposition of each of its human cellular or tissue-based product as part of its tracking method. Section 1271.290(f) would require an establishment to document that a consignee agreed to participate in its tracking method and will take all necessary steps to ensure compliance with the requirements of the regulation. Section 1271.320(b) would require an establishment to maintain a record of each complaint that it receives, including a review and evaluation. Section 1271.350(c) would require the documentation of adverse reaction reports, errors and accidents in manufacturing that may lead to product deviation reports, and the investigation of these reports.

Description of Respondents: Manufacturers of cellular and tissue-based products.

FDA estimates the burden of this collection of information as follows:

TABLE 11.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
1271.155(a)	1,065	1	1,065	3	3,195
1271.270(c)	1,065	1	1,065	1	1,065
1271.290(c)	791	250	19,8215	0.08	15,857
1271.290(f)	1,065	1	1,065	1	1,065
1271.350(a)	1,065	6	6,390	0.5	3,195
1271.350(b)	1,065	2	2,130	0.5	1,065
1271.370(a)(2) and (a)(3)	633	207	131,005	0.25	32,751
Total					58,193

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 12.—ESTIMATED ANNUAL RECORDKEEPING BURDEN[1]

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
One-time Burden (Creation of SOP's[2])	1,065	9	9,585	16	153,360
One-time Burden (Review of existing SOP's for compliance)	1,065	19	20,235	5	101,175
SOP Maintenance (See previous list of 19 SOP's)	1,065	19	20,235	1	20,235
1271.155(f)	1,065	1	1,065	0.25	266
1271.160(b)(3)	483	2	966	6	5,796
1271.160(b)(7)	597	15	8,955	0.5	4,478
1271.160(d)(3)	558	1	558	13	7,254
1271.160(e)	597	5	2,985	0.25	746
1271.170(d)	483	1	483	1	483
1271.180	483	1	483	120	57,960
1271.190(c)(4)	558	12	6,696	1	6,696
1271.195(c)	822	12	9,864	1	9,864
1271.200(e)	483	12	5,796	1	5,796
1271.210(c)	597	12	7,164	1	7,164
1271.220(b) and (d)	91	781	71,070	0.08	5,686
1271.225(b)	1,065	2	2,130	1	2,130
1271.230(a)	755	1	755	1	755
1271.230(b)	980	1	980	1	980
1271.230(e)	1,065	1	1,065	1	1,065
1271.260(b)(3)	597	356	212,532	0.08	17,003
1271.260(d)	747	12	8964	0.25	2,241
1271.265(a)	597	360	214,920	0.08	17,194
1271.265(b)	822	407	334,554	0.08	26,764
1271.270(a) and (c)	597	360	214,920	0.1	21,492
1271.270(f)	755	2	1,510	0.25	378
1271.290(e)	641	306	196,146	0.3	58,844
1271.290(f)	1,065	57	60,705	0.35	21,247
1271.320(b)	830	5	4,150	1	4,150
1271.350(c)	726	6	4,356	0.5	2,178
Total					563,380

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] Standard operating procedures.

Under this proposed rule, 19 SOP's would be required as previously described. FDA is assuming that approximately 1,065 manufacturers would have to create up to 9 SOP's for a total of 9,585 records, and the agency estimates that it would take 16 hours per record to create 9 new SOP's for a total of 153,360 hours as a one-time burden. The agency estimates that up to 19 SOP's would already exist as a result of complying with current applicable regulations or following industry organizational standards. Approximately 1,065 manufacturers would have to review these 19 SOP's for compliance with the regulations, which would expend approximately

5 hours per SOP as a one-time burden. Annual SOP maintenance of existing SOP's is estimated to involve 1 hour annually per SOP, totaling 19 hours annually per recordkeeper.

In some cases, the estimated burden may appear to be lower or higher than the burden experienced by individual establishments. The estimated burden in these charts is an estimated average burden, taking into account the range of impact each proposed regulation may have. In estimating the burden, FDA compared the proposed regulations with the current voluntary standards of a number of industry organizations, such as, AATB, EBAA, AABB, FAHCT, and CAP, and the guidelines provided by ASRM. In those cases where a voluntary industry standard appears to be equivalent to a proposed regulation, FDA has assumed that any reporting or recordkeeping burden is a customary and usual business practice of establishments who are members of those organizations and no additional burden is calculated here. In some cases establishments affected by this proposed rule may already be required to comply with regulations for manufacturers of human drugs or biological products, e.g., parts 210, 211, 312, 314, and 606 (21 CFR parts 312, 314, and 606).

FDA has estimated the reporting (table 11) and recordkeeping (table 12) burdens based upon the agency's institutional experience with comparable recordkeeping and reporting provisions applicable to the human drug and biological product industries, recent information from trade organizations related to the manufacturing of products utilizing cells and tissues, and data provided by the Eastern Research Group (ERG), a consulting firm hired by FDA to prepare an economic analysis of the potential economic impact on sperm banks and ART facilities.

The agency has estimated that there are approximately 1,065 manufacturers of cellular and tissue-based products (approximately 110 manufacturers of conventional tissue, 114 manufacturers of eye tissue, 425 manufacturers of peripheral and cord blood stem cells, 350 manufacturers of reproductive tissue, and 66 manufacturers of cellular or tissue-based licensed biological products or devices). FDA obtained these estimates of manufacturers (including percentage of members and nonmembers) from the various trade organizations and the agency's registration systems for

biological product and device manufacturers. The total number of respondents and recordkeepers, 1,065, in the tables is decreased for each provision by the number of establishments that follow, as usual and customary practice, the applicable established trade organizational standards comparable to the CGTP requirements, i.e., AATB, EBAA, FAHCT, AABB, or CAP. FDA based the estimated numbers for ''Number of Respondents'' and ''Number of Recordkeepers'' on information provided by the trade organizations.

FDA based the estimated numbers for ''Annual Frequency per Response,'' ''Total Annual Responses,'' ''Annual Frequency per Recordkeeping,'' and ''Total Annual Records'' on information received from the trade organizations, institutional experience with similar requirements (good manufacturing practice), general information provided to FDA during inspections of manufacturers of human tissue intended for transplantation, and information gathered by ERG.

The estimates for ''Hours per Response'' or ''Hours per Recordkeeper'' were calculated using comparable burdens under drug GMP regulations, part 211, and GMP for blood and blood components, part 606, or by using the information provided by ERG, e.g., time spent on §§ 1271.190(c)(4) (documentation of cleaning and sanitation) and 1271.195(c) (documentation of environmental control and monitoring activities) was an estimate provided by ERG.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d), the agency has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons are requested to send comments regarding information collection by [*insert date 30 days after date of publication in the* **Federal Register**] to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Wendy Taylor, Desk Officer for FDA.

XI. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has concluded that the proposed rule raises Federalism implications because it could preempt some States' laws regarding donated human cells and tissues. FDA currently

is seeking comments from elected State and local government officials under Executive Order 13132 on: (1) The need for the proposed good tissue practice rule to prevent communicable disease transmission through human cellular and tissue-based products; (2) alternatives that would limit the scope of such national requirements or otherwise preserve State prerogatives and authority; (3) the proposed good tissue practice provisions; and (4) any other issues raised by this proposed rule possibly affecting State laws and authorities.

XII. Request For Comments

Interested persons may submit to the Dockets Management Branch (address above) written comments on this proposal by [*insert date 120 days after date of publication in the* **Federal Register**]. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday. Comments received in response to the proposed GTP rule could support a change that will affect language in previously published proposed tissue rules. In the event that any tissue rule becomes effective before either or both of the remaining tissue rules become effective, FDA intends to make conforming amendments to those final rules at the same time the remaining tissue rules become effective.

List of Subjects in 21 CFR Part 1271

Human cellular and tissue-based products, Communicable diseases, HIV/AIDS, Reporting and recordkeeping requirements.

Therefore, under the Public Health Service Act, and under the authority delegated to the commissioner of Food and Drugs, it is proposed to amend 21 CFR Chapter I as follows:

Part 1271 as proposed in the Federal Register of May 14, 1998 (63 FR 26744) and September 30, 1999 (64 FR 52696) is amended as follows:

PART 1271—HUMAN CELLULAR AND TISSUE–BASED PRODUCTS

1. The authority citation for 21 CFR part 1271 is revised to read as follows:

Authority: 42 U.S.C. 216, 243, 263a, 264, 271.

2. Section 1271.3 is amended by adding paragraphs (ff) through (tt) to read as follows:

§ 1271.3 Definitions.

* * * * *

(ff) *Available for distribution* means that the human cellular or tissue-based product has been determined to meet all release specifications and to be suitable for distribution.

(gg) *Adverse reaction* means a noxious and unintended response to any human cellular or tissue-based product for which there is a reasonable possibility that the response may have been caused by the product (i.e., the relationship cannot be ruled out).

(hh) *Processing material* means any material or substance that is used in, or to facilitate, processing, but which is not intended by the manufacturer to be included in the human cellular or tissue-based product when it is made available for distribution.

(ii) *Complaint* means any written, oral, or electronic communication that alleges:

(1) That a human cellular or tissue-based product has transmitted or may have transmitted a communicable disease to the recipient of the product;

(2) That the function or integrity of a human cellular or tissue-based product may have been impaired; or

(3) Any other problem with a human cellular or tissue-based product that could result from the failure to comply with current good tissue practice.

(jj) *Distribution* means any conveyance or shipment of human cellular or tissue-based products (including importation and exportation), whether or not such conveyance or shipment is entirely intrastate and whether or not possession of the product is taken.

(kk) *Product deviation* means an event that represents a deviation from current good tissue practice, applicable standards, or established specifications; or an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease agent or disease from a human cellular or tissue-based product to a recipient, or may lead to product contamination, or may adversely affect the function or integrity of the product.

(ll) *Establish and maintain* means define, document (in writing or electronically), and implement, then follow, review, and as needed, revise on an ongoing basis.

(mm) *Processing* means any activity other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution performed on a human cellular or tissue-based product, including but not limited to preparation, sterilization, steps to inactivate and remove adventitious agents, preservation for storage, and removal from storage.

(nn) *Quality audit* means a documented, independent inspection and review of an establishment's activities, including manufacturing and tracking, performed according to procedures, to verify, by examination and evaluation of objective evidence, the degree of compliance with those aspects of the quality program under review.

(oo) *Quality program* means an organization's comprehensive system for manufacturing and tracking human cellular and tissue-based products. This program includes preventing, detecting, and correcting deficiencies that may lead to circumstances that increase the risk of introduction, transmission, or spread of communicable disease.

(pp) *Recovery* means the process of obtaining from a donor cells or tissues that are intended for use in human implantation, transplantation, infusion, or transfer.

(qq) *Storage* means holding human cellular or tissue-based products for future processing and/ or distribution.

(rr) *Validation* means confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. Validation of a process, or process validation, means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.

(ss) *Verification* means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

(tt) *Importer of record* means the person, establishment, or its representative responsible for making entry of imported goods in accordance with all laws affecting such importation.

3. Subpart D, consisting of §§ 1271.150 through 1271.320, is added to part 1271 to read as follows:

Subpart D—Current Good Tissue Practice

Sec.

Subpart D—Current Good Tissue Practice

§ 1271.150 Current good tissue practice: general.

(a) *General.* Current good tissue practice (CGTP) requirements are set forth in this subpart and in subpart C of this part. CGTP requirements govern the methods used in, and the facilities and controls used for, the manufacture of human cellular and tissue-based products, including but not limited to all steps in recovery, donor screening, donor testing, processing, storage, labeling, packaging, and distribution. The CGTP requirements are intended to prevent the introduction, transmission, and spread of communicable disease through the use of human cellular and tissue-based products by helping to ensure that the products do not contain communicable disease agents; that the products do not become contaminated during manufacturing; and that the function and integrity of the products are not impaired through improper manufacturing. The CGTP provisions specifically governing determinations of donor suitability, including donor screening and testing, are set out separately in subpart C of this part.

(b) *Compliance with applicable requirements.* (1) If an establishment engages in only some operations subject to the regulations in this subpart and subpart C of this part, and not others, that establishment need only comply with those requirements applicable to the operations in which it engages. However, an establishment that engages another establishment under a contract, agreement, or other arrangement, to perform any step in the manufacturing process, is responsible for ensuring that the work is performed in compliance with the requirements in this subpart and subpart C of this part.

(2) The establishment that determines that a product meets release criteria and makes the product available for distribution, whether or not that establishment is the actual distributor, is responsible for ensuring that the product has been manufactured in compliance with the requirements of subparts C and D of this part and any other applicable requirements.

(c) *Compliance with parts 210, 211, and 820 of this chapter.* With respect to human cellular or tissue-based products regulated as biological drugs or devices under section 351 of the Public Health Service Act and/or the Federal Food, Drug, and Cosmetic Act, the procedures contained in this subpart and in subpart C of this part and the current good manufacturing practice regulations in parts 210 and 211 of this chapter and the quality system regulations in part 820 of this chapter, shall be considered to supplement, not supersede, each other unless the regulations explicitly provide otherwise. In the event that it is impossible to comply with all applicable regulations in these parts, the regulations specifically applicable to the biological drug or device in question shall supersede any other requirements.

(d) *Where appropriate.* When a requirement is qualified by ''where appropriate,'' it is deemed to be ''appropriate'' unless the establishment can document justification otherwise. A requirement is ''appropriate'' if nonimplementation could reasonably be expected to result in the product's not meeting its specified requirements related to prevention of introduction, transmission, or spread of communicable disease agents and diseases, or in the establishment's inability to carry out any necessary corrective action.

§ 1271.155 Exemptions and alternatives.

(a) *General.* An establishment may request an exemption or alternative from any requirement in subpart C or D of this part regarding a human cellular or tissue-based product.

(b) *Request for exemption or alternative.* A request under this section shall be submitted to the Director, Center for Biologics Evaluation and Research (the Director). The request shall be accompanied by supporting documentation, including all relevant valid scientific data. A request

for an exemption shall contain information justifying the exemption. A request for an alternative shall contain a description of an alternative that satisfies the purpose of the requirement.

(c) *Criteria for granting exemption or alternative.* The Director may grant an exemption or alternative if he or she finds that such action is consistent with the goals of preventing the introduction, transmission, and spread of communicable disease and that:

(1) The information submitted justifies an exemption; or

(2) The proposed alternative satisfies the purpose of the requirement.

(d) *Form of request.* A request for an exemption or alternative shall ordinarily be made in writing or electronically. However, in limited circumstances such a request may be made orally, and an exemption or alternative may be granted orally by the Director. An oral request and approval shall be followed by an immediate written request and written acknowledgment of approval.

(e) *Operation under exemption or alternative.* An establishment shall not begin operating under the terms of a requested exemption or alternative until the exemption or alternative has been granted in writing. An establishment may apply for an extension of an exemption or alternative beyond its expiration date, if any.

(f) *Documentation.* An establishment operating under the terms of an exemption or alternative shall maintain documentation of:

(1) FDA's granting of the exemption or alternative, and

(2) The date on which it began operating under the terms of the exemption or alternative.

§ 1271.160 Establishment and maintenance of a quality program.

(a) *General.* An establishment that performs any step in the manufacture of human cellular and tissue-based products shall establish and maintain a quality program that is appropriate for the specific human cellular and tissue-based products manufactured and the manufacturing steps performed and that meets the requirements of this subpart.

(b) *Functions.* Functions of the quality program shall include, but not be limited to:

(1) Ensuring that appropriate procedures are established and maintained, and ensuring compliance with the requirements of § 1271.180 with respect to procedures, including review, approval, revision, and archiving;

(2) Ensuring that procedures exist for receiving, investigating, evaluating, and documenting information received from other sources and for sharing with consignees and other establishments that are known to have recovered cells or tissue from the same donor any information pertaining to the integrity and function of a human cellular or tissue-based product, possible contamination of the product, or the potential transmission of communicable disease by the product. In the case of information received after the product is made available for distribution or shipped to the consignee, procedures shall include provisions for evaluating the effect this information has on the product and for the notification of all entities to whom affected product was distributed, the quarantine and recall of the product, and/or reporting to FDA, as necessary.

(3) Ensuring that appropriate corrective actions, including reaudits of deficiencies, are taken and documented, as necessary. Corrective actions shall be verified to ensure that such actions are effective and do not adversely affect the finished product. Where appropriate, corrective actions shall include both short-term action to address the immediate problem and long-term action to prevent the problem's recurrence. Documentation of corrective actions shall include where appropriate:

(i) Identification of the human cellular or tissue-based product affected and a description of its disposition;

(ii) The nature of the problem requiring corrective action;

(iii) A description of the corrective action taken; and

(iv) The date(s) of the corrective action.

(4) Ensuring the proper training and education of personnel;

(5) Establishing and maintaining appropriate monitoring systems as necessary to comply with the requirements of this subpart (e.g., environmental monitoring);

(6) Establishing and maintaining a system for the maintenance of records in compliance with § 1271.270;

(7) Investigating and documenting all product deviations and making reports if required under § 1271.350(b) or other applicable regulations. Each investigation shall include a review and evaluation of the product deviation, the efforts made to determine the cause, and the implementation of corrective action(s) designed to address the product deviation and prevent recurrence. Each establishment shall also perform a periodic review and analysis of all product deviations, at least once each year, for the purpose of identifying trends and adopting appropriate preventive measures. This analysis shall be available for review upon inspection and for submission to FDA upon request; and

(8) Conducting evaluations, investigations, audits, and other actions necessary to ensure compliance with the requirements of this subpart.

(c) *Authority over program.* One or more designated persons shall have authority over and responsibility for ensuring that the quality program is effectively established and effectively maintained. This person shall report to management on the performance of the quality program on no less than an annual basis. If this person also performs other tasks in the establishment, he or she shall not have final oversight over his or her own work.

(d) *Audits.* (1) A comprehensive quality audit, as defined in § 1271.3(nn), shall be performed no less than once in a 12-month period. Special audits shall be performed as necessary. All audits shall be conducted in accordance with procedures to assure that the quality program is operating effectively and to identify trends or recurring problems.

(2) Quality audits shall be conducted by individuals with sufficient knowledge, training, and experience to identify problems in the specific processes under review, but who do not have direct responsibility for the processes being audited.

(3) A documented report of the results of the audits and reaudits, where taken, shall be retained. Such reports shall be reviewed by management having responsibility for the matters audited, and this management review shall be documented.

(e) *Computers.* If computers or automated data processing systems are used as part of the quality program, as part of manufacture or tracking, or for maintaining data or records related to the manufacture or tracking of human cellular or tissue-based products, the establishment shall validate computer software for its intended use according to an established protocol. All software changes shall be validated before approval and issuance. These validation activities and results shall be documented.

(f) *Procedures.* Procedures shall be established and maintained for a quality program, including quality audits.

§ 1271.170 Organization and personnel.

(a) *General.* Each establishment shall maintain an adequate organizational structure and sufficient personnel to ensure that the requirements of this part are met.

(b) *Competent performance of functions.* Each establishment shall have sufficient personnel with the necessary education and experience to assure competent performance of their assigned functions. Personnel shall perform only those activities for which they are qualified.

(c) *Training.* All personnel shall be trained, and retrained as necessary, to perform their assigned responsibilities adequately. Personnel shall be made aware of possible consequences of improper performance of their duties; e.g., the risk of transmission of communicable disease agents and diseases, and the hazards associated with those disease agents and diseases, and the risk of adversely affecting function and integrity of human cellular and tissue-based products.

(d) *Records.* A record of the education, experience, training, and retraining shall be maintained for all personnel.

§ 1271.180 Procedures.

Each establishment shall establish and maintain procedures for all significant steps that it performs in the manufacture of human cellular and tissue-based products. These procedures shall be designed to prevent circumstances that increase the risk of the introduction, transmission, and spread of communicable disease through the use of human cellular and tissue-based products by ensuring that the products do not contain relevant communicable disease agents; that the products do not become contaminated during manufacturing; and that the function and integrity of the products are not impaired through improper manufacturing. Procedures shall be designed to ensure compliance with the requirements of this part. Prior to implementation, all procedures shall be reviewed and approved by a responsible person. At least once in a 12-month period, all procedures shall be reviewed and, if necessary, revised, and the review shall be documented. Procedures shall be readily available to the personnel in the area where the operations to which they relate are performed, unless this is impractical. Any deviation from a procedure shall be authorized in advance by a responsible person, recorded, and justified. An establishment may adopt current standard procedures, such as those in a technical manual prepared by another organization, provided the procedures are consistent with and at least as stringent as the requirements of this part and appropriate for the operations conducted at the establishment. Obsolete procedures shall be archived for at least 10 years.

§ 1271.190 Facilities.

(a) *General.* Any facility used in the manufacture of human cellular or tissue-based products shall be of suitable size, construction, and location to facilitate cleaning, relevant maintenance, and proper operations. The facility shall be maintained in a good state of repair. Adequate lighting, ventilation, plumbing, drainage, and washing and toilet facilities shall be provided.

(b) *Operations.* A facility used in the manufacture of human cellular or tissue-based products shall be divided into separate or defined areas of adequate size for each operation that takes place in the facility, or other control systems shall be established and maintained to prevent improper

labeling, mix-ups, contamination, cross-contamination, and accidental exposure of human cellular and tissue-based products to communicable disease agents.

(c) *Facility cleaning and sanitation.* (1) Any facility used in the manufacture of human cellular and tissue-based products shall be maintained in a clean, sanitary, and orderly manner.

(2) Sewage, trash, and other refuse shall be disposed of in a timely, safe, and sanitary manner.

(3) Procedures for facility cleaning and sanitation shall be established and maintained. These procedures shall assign responsibility for sanitation and shall describe in sufficient detail the cleaning methods to be used and the schedule for cleaning the facility.

(4) All significant cleaning and sanitation activities shall be documented, and records shall be maintained.

§ 1271.195 Environmental control and monitoring.

(a) *General.* Where environmental conditions could reasonably be expected to have an adverse effect on the function or integrity of human cellular and tissue-based products, or to cause contamination or cross-contamination of products or equipment or accidental exposure of products to communicable disease agents, procedures shall be established and maintained to adequately control and monitor environmental conditions and to provide proper conditions for operations. Where appropriate, these procedures shall provide for the following control and monitoring activities or systems:

(1) Temperature and humidity controls;

(2) Ventilation and air filtration;

(3) Cleaning and disinfecting of rooms and equipment to ensure aseptic processing operations;

(4) Maintenance of equipment used to control conditions necessary for aseptic processing operations; and

(5) Environmental monitoring for organisms.

(b) *Inspections*. Each environmental control system shall be inspected periodically to verify that the system, including necessary equipment, is adequate and functioning properly. Appropriate corrective action shall be taken as necessary.

(c) *Records*. Environmental control and monitoring activities shall be documented, and records shall be maintained.

§ 1271.200 Equipment.

(a) *General*. Equipment used in the manufacture of human cellular and tissue-based products shall be of appropriate design for its use, shall be suitably located and installed to facilitate operations, including cleaning and maintenance, and shall not have any adverse effect on the products. Any automated, mechanical, electronic, computer, or other equipment used for inspection, measuring, and testing shall be capable of producing valid results.

(b) *Procedures and schedules*. Procedures shall be established and maintained for cleaning, sanitizing, and maintaining equipment to prevent malfunctions, contamination or cross-contamination, accidental exposure of human cellular and tissue-based products to communicable disease agents, and other events that could reasonably be expected to have an adverse effect on product function or integrity. Cleaning, sanitizing, and maintenance of equipment shall be performed according to established schedules.

(c) *Calibration of equipment*. All automated, mechanical, electronic, computer, or other equipment used for inspection, measuring, and testing shall be routinely calibrated according to established procedures and schedules. Calibration procedures shall include specific directions and, where applicable, shall include limits for accuracy and precision. When accuracy and precision limits are not met, there shall be provisions for corrective action to reestablish the limits and to evaluate whether there were any adverse effects on any human cellular or tissue-based product.

(d) *Inspections*. Equipment shall be routinely inspected for cleanliness, sanitation, and calibration, and to assure adherence to applicable equipment maintenance schedules.

(e) *Records*. All maintenance, cleaning, sanitizing, calibration, and other activities performed in accordance with this section shall be documented and maintained. Records of recent maintenance, cleaning, sanitizing, calibration, and other activities shall be available at each piece of equipment. Records of the use of each piece of equipment, which shall include the identification of each human cellular or tissue-based product manufactured with that equipment, shall be maintained.

§ 1271.210 Supplies and reagents.

(a) *Receipt and verification*. Procedures shall be established and maintained for receiving supplies and reagents used in the manufacture of human cellular and tissue-based products. Supplies and reagents shall be verified to meet specifications designed to prevent circumstances that increase the risk of the introduction, transmission, or spread of communicable disease through product contamination or the impairment of product function or integrity, and shall not be used until such verification is completed. Verification may be accomplished by the establishment that uses the supply or reagent, or by the vendor of the supply or reagent.

(b) *Reagents*. Reagents used in processing and preservation of human cellular and tissue-based products shall be of appropriate grade for the intended use and shall be sterile, if appropriate. Procedures for production of in-house reagents shall be validated and/or verified.

(c) *Records*. The following records pertaining to supplies and reagents shall be maintained:

(1) Records of the receipt of each supply or reagent, including the type, manufacturer, lot number, date of receipt, and expiration date;

(2) Records of the verification of each supply or reagent, including test results or, in the case of vendor verification, a certificate of analysis from the vendor; and

(3) Records of the use of each supply or reagent, which shall include the identification of each human cellular or tissue-based product manufactured with the supply or reagent.

§ 1271.220 Process controls.

(a) *General.* Each establishment engaged in the processing of human cellular or tissue-based products shall develop, conduct, control, and monitor its manufacturing processes to ensure that each human cellular or tissue-based product conforms to specifications, is not contaminated, maintains its function and integrity, and is manufactured so as to prevent transmission of communicable disease by the product.

(b) *Processing material.* Where a processing material could reasonably be expected to have an adverse effect on a human cellular or tissue-based product's function or integrity, the establishment shall establish and maintain procedures for the use and removal of such processing material to ensure that it is removed or limited to an amount that does not adversely affect the product's function or integrity. The removal or reduction of such processing material shall be documented.

(c) *Pooling.* Human cells or tissue from two or more donors shall not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing.

(d) *In-process monitoring.* Procedures shall be established and maintained, where appropriate, to ensure that specified requirements of in-process product are met. Such procedures shall ensure that in-process product is controlled until the required inspection and tests or other verification activities have been completed or necessary approvals are received and documented. Sampling of in-process products shall be representative of the material to be evaluated.

§ 1271.225 Process changes.

(a) *Procedures.* Procedures shall be established and maintained for making changes to a process. Any such change shall be verified or validated, to ensure that the change does not create an adverse impact elsewhere in the operation, and shall be approved before implementation by a responsible person with appropriate knowledge and background.

(b) *Change records.* All changes to established processes shall be documented, including the rationale for the change and the date of implementation. Change records shall include a description

of the change, identification of the affected documents, the signature of the approving individual(s), approval date, and when the change becomes effective. Approved changes shall be communicated to the appropriate personnel in a timely manner.

§ 1271.230 Process validation.

(a) *General.* Where the results of a process cannot be fully verified by subsequent inspection and tests, the process shall be validated and approved according to established procedures. The validation activities and results, including the date and signature of the individual(s) approving the validation, shall be documented.

(b) *Claims.* Any process-related claim in labeling or promotional materials for a human cellular or tissue-based product, e.g., a claim for sterility or viral inactivation, shall be based on a validated process. Validation shall be documented, and the documentation shall be maintained at the establishment and made available for review on inspection.

(c) *Dura mater.* Dura mater shall be processed using a validated procedure that reduces transmissible spongiform encephalopathy, while preserving the clinical utility of the product.

(d) *Procedures.* Procedures shall be established and maintained for monitoring and control of validated processes to ensure that the specified requirements continue to be met.

(e) *Changes and deviations.* When changes to or deviations from a validated process occur, the establishment shall review and evaluate the process and perform revalidation where appropriate. These activities shall be documented.

§ 1271.250 Labeling controls.

Procedures shall be established and maintained to control the labeling of human cellular and tissue-based products. These procedures shall be designed to ensure proper product identification and to prevent mix-ups. Procedures shall include verification of label accuracy, legibility, and integrity. Procedures shall ensure that each product is labeled in accordance with all applicable labeling requirements, including those in §§ 1271.55, 1271.65, 1271.75, 1271.90, 1271.290, and

1271.370, and that each product made available for distribution is accompanied by documentation of the donor suitability determination as required under § 1271.55.

§ 1271.260 Storage.

(a) *Control of storage areas.* Each establishment shall control its storage areas and stock rooms to prevent mix-ups, commingling, deterioration, contamination, and cross-contamination, of human cellular and tissue-based products and supplies, and any other condition that may adversely affect product function or integrity, and to prevent improper release for distribution.

(b) *Temperature.* (1) Each establishment shall store human cellular and tissue-based products at an appropriate temperature and for no longer than the maximum storage period for the product.

(2) Acceptable temperature limits for storage of human cellular and tissue-based products at each step of the manufacturing process shall be established to ensure product function and integrity, to prevent product deterioration, and to inhibit the growth of infectious agents.

(3) Storage temperatures for human cellular and tissue-based products shall be maintained and recorded. Recorded temperatures shall be reviewed periodically to assure that temperatures have not exceeded acceptable limits.

(c) *Expiration date.* Where appropriate, an expiration date shall be assigned to each human cellular or tissue-based product based on the following factors:

(1) Product type;

(2) Processing procedures, including the method of preservation;

(3) Storage conditions; and

(4) Packaging.

(d) *Corrective action.* Corrective action shall be taken and documented whenever proper storage conditions are not met.

§ 1271.265 Receipt and distribution.

(a) *General.* Procedures shall be established and maintained for the following activities: receipt, acceptance or rejection, distribution, and destruction or other disposition of human cellular or tissue-based products, and these activities shall be documented. Documentation shall include:

(1) Identification of the human cellular or tissue-based product;

(2) Activities performed and the results of such activities;

(3) Date(s) of activity;

(4) Quantity of human cellular or tissue-based product subject to the activity; and

(5) Disposition of the human cellular or tissue-based product (e.g., identity of consignee).

(b) *Receiving activities.* Procedures shall be established and maintained for receiving and accepting or rejecting human cellular or tissue-based products for processing, distribution, or any other step in the manufacturing process. The status of each incoming human cellular or tissue-based product (e.g., with respect to quarantine, donor screening and testing, and processing) shall be determined and identified promptly after receipt, and each product shall be handled in a manner appropriate to its status. Each incoming human cellular or tissue-based product shall be inspected according to established procedures for damage, contamination, deterioration, or other indications that the integrity of the product has been impaired. Acceptance or rejection of incoming products shall be documented.

(c) *Availability for distribution.* Procedures shall be established and maintained for making human cellular and tissue-based products available for distribution. These procedures, which shall include release criteria, shall be designed to prevent the release of products that are in quarantine, are contaminated, have deteriorated, or otherwise have been manufactured in violation of current good tissue practice and, except as provided under §§ 1271.65 and 1271.90, products from donors who have been determined to be unsuitable or for whom a donor-suitability determination has not been completed. Prior to making a human cellular or tissue-based product available for distribution, the establishment shall verify and document that the release criteria have been met

and shall review all records pertaining to the product. The determination that a human cellular or tissue-based product is available for distribution shall be documented and dated by a responsible person.

(d) *Packaging.* Packaging and shipping containers shall be designed, validated, and constructed to ensure product function and integrity and protect the product from damage, deterioration, contamination, or other adverse effects during customary conditions of processing, storage, handling, and distribution.

(e) *Shipping conditions.* Appropriate shipping conditions shall be defined for each type of human cellular or tissue-based product to be maintained during transit.

(f) *Return to inventory.* Procedures shall be established and maintained to determine if a product that is returned to an establishment is suitable to be returned to inventory.

§ 1271.270 Records.

(a) *General.* Records shall be maintained concurrently with the performance of each significant step required in this subpart and subpart C of this part. Any requirement in this part that an action be documented involves the creation of a record, which record is subject to the requirements of this section. All records shall be accurate, indelible, and legible. The records shall identify the person performing the work, the dates of the various entries, and shall be as detailed as necessary to provide a complete history of the work performed and to relate the records to the particular human cellular or tissue-based product involved. Record security systems shall be adequate to ensure the confidentiality of donors and recipients of human cellular and tissue-based products.

(b) *Records management system.* A records management system shall be established and maintained. Under this system, records pertaining to a particular human cellular or tissue-based product manufactured shall be maintained in such a way as to facilitate review of the product's history prior to making it available for distribution and, if necessary, subsequent to the product's release as part of a follow-up evaluation or investigation. Records pertinent to the manufacture of each type of human cellular or tissue-based product (e.g., procedures, specifications, labeling

and packaging procedures, equipment logs) shall also be maintained and organized under the records management system. If records are maintained in more than one location, then the records management system shall be designed to ensure prompt identification, location, and retrieval of all records.

(c) *Other recordkeeping requirements.* Procedures shall be established and maintained to ensure compliance with the recordkeeping requirements in § 1271.55. Documentation of results and interpretation of all testing for relevant communicable disease agents in compliance with § § 1271.80 and 1271.85 shall be maintained, as well as the name and address of the testing laboratory or laboratories. Documentation of the results and interpretation of all donor screening for relevant communicable disease in compliance with § 1271.75 shall be maintained in accordance with § 1271.270. Documentation of the donor-suitability determination, including the name of the responsible person who made the determination and the date of the determination, shall also be maintained. Information on the identity and relevant medical records of the donor, as defined in § 1271.3(v), shall be in English or, if in another language, shall be translated to English and accompanied by a statement of authenticity by the translator that specifically identifies the translated document.

(d) *Methods of retention.* Records required under this subpart may be maintained electronically, as original paper records, or as true copies such as photocopies, microfiche, or microfilm, in which case suitable reader and photocopying equipment shall be readily available. Records stored in automated data processing systems shall be backed up. Electronic records and electronic signatures are subject to the requirements in part 11 of this chapter.

(e) *Length of retention.* All records shall be retained 10 years after their creation. However, records pertaining to a particular human cellular or tissue-based product shall be retained at least 10 years after the date of implantation, transplantation, infusion, or transfer of the product, or if the date of implantation, transplantation, infusion , or transfer is not known, then records shall be retained at least 10 years after the date of the product's distribution, disposition, or expiration,

whichever is latest. Records for archived specimens of dura mater shall be retained 10 years after the appropriate disposition of the specimens. The establishment shall make provisions for all records to be maintained for the required period in the event that the establishment ceases operation.

(f) *Contracts and agreements.* Each establishment shall maintain records of any contract, agreement, or other arrangement with another establishment under which any step in the manufacturing process is performed by the other establishment. These records shall include the name and address of the other establishment and the responsibilities of each party to the contract, agreement, or other arrangement.

§ 1271.290 Tracking.

(a) *General.* Each establishment that performs any step in the manufacture of a human cellular or tissue-based product shall track each such product in accordance with this section.

(b) *Method of product tracking.* (1) Each establishment shall establish and maintain a method of product tracking that enables the tracking of all human cellular and tissue-based products from:

(i) The donor to the recipient or final disposition; and

(ii) The recipient or final disposition to the donor.

(2) Alternatively, an establishment that performs some but not all of the steps in the manufacture of a human cellular or tissue-based product may participate in a method of product tracking that has been established and is maintained by another establishment responsible for other steps in the manufacture of the same product, provided that the tracking method complies with all the requirements of this section.

(c) *Distinct identification code.* As part of its tracking method, an establishment shall ensure that each human cellular and tissue-based product that it manufactures is assigned and labeled with a distinct identification code, e.g., alphanumeric, that relates the product to the donor and to all records pertaining to the product. Except in the case of autologous or directed donations, such a code must be created specifically for tracking and may not include an individual's name, social security or medical record number. An establishment may adopt a distinct identification

code assigned by another establishment engaged in the manufacturing process, or may assign a new code. An establishment that assigns a new code to a product shall establish and maintain procedures for relating the new code to the old code.

(d) *Product information.* As part of its tracking method, an establishment shall ensure that the identifier and type of each human cellular or tissue-based product that is implanted, transplanted, infused, or transferred into a recipient is recorded in the recipient's medical records, or in other pertinent records, to enable tracking from the recipient to the donor.

(e) *Recipient information.* As part of its tracking method, an establishment shall document, and maintain records of, the disposition of each of its human cellular or tissue-based products, to enable tracking from the donor to the recipient or final disposition. The information to be maintained shall permit the prompt identification of the recipient of the product, if any.

(f) *Consignees.* At or before the time of distribution of a human cellular or tissue-based product to a consignee, an establishment shall inform the consignee in writing of the requirements in this section and of the tracking method that the establishment has established and is maintaining to comply with these requirements. Upon initial distribution of product to the consignee, the establishment shall document that the consignee agreed to participate in its tracking method and to take all necessary steps to ensure compliance with the requirements of this section.

(g) *Requirements specific to dura mater donors.* Appropriate specimens from each donor of dura mater shall be archived, under appropriate storage conditions, and for the appropriate duration, to enable testing of the archived material for evidence of transmissible sponiform encephalopathy, and appropriate disposition of any affected dura mater tissue, if necessary.

§ 1271.320 Complaint file.

(a) *Procedures.* Each establishment shall establish and maintain procedures for the prompt review, evaluation, and documentation of all complaints, as defined in § 1271.3(ii), and the investigation of complaints as appropriate.

(b) *Complaint file.* Each establishment shall maintain a record of each complaint that it receives in a file designated for complaints. The complaint file shall contain sufficient information about each complaint for proper review and evaluation of the complaint, including the identifier of the human cellular or tissue-based product that is the subject of the complaint. The complaint file shall be made available for review and copying upon request from an authorized employee of the Food and Drug Administration.

(c) *Review and evaluation of complaints.* Each complaint shall be reviewed and evaluated to determine if the complaint is related to a product deviation of a human cellular or tissue-based product or to an adverse reaction, and to determine if a report under § 1271.350 or another applicable regulation is required. Each complaint that represents an event required to be reported to FDA shall be promptly reviewed, evaluated, and investigated. A complaint that does not represent an event required to be reported shall be reviewed and evaluated to determine whether investigation is necessary; investigation may include referring a copy of the complaint to another establishment that performed manufacturing steps pertinent to the complaint. When no investigation is made, the establishment shall maintain a record that includes the reason no investigation was made, and the name of the individual responsible for the decision not to investigate.

4. Subpart E, consisting of §§ 1271.330 through 1271.370, is added to part 1271 to read as follow:

Subpart E—Additional Requirements for Establishments Described in § 1271.10

Sec.

Subpart E—Additional Requirements for Establishments Described in § 1271.10

§ 1271.330 Applicability

The provisions set forth in this subpart are applicable only to human cellular and tissue-based products described in § 1271.10 and regulated solely under section 361 of the Public Health Service Act (the PHS Act) and the regulations in this part, and to the establishments that manufacture those products. Human cellular and tissue-based products described in § 1271.15 and regulated as drugs, devices, and/or biological products under the act and/or section 351 of the PHS Act, and the establishments that manufacture those products, are not subject to the regulations set forth in this subpart.

§ 1271.350 Reporting.

(a) *Adverse reaction reports.* (1) Any establishment that receives information about an adverse reaction, regardless of source, shall review the information to determine whether the adverse reaction is required to be reported. The establishment shall report any adverse reaction involving the transmission of a communicable disease, product contamination, or failure of the product's function or integrity if the adverse reaction:

(i) Is fatal;

(ii) Is life-threatening;

(iii) Results in permanent impairment of a body function or permanent damage to body structure; or

(iv) Necessitates medical or surgical intervention. Each report shall be submitted on an FDA Form-3500A to the address in paragraph (a)(4) of this section within 15 calendar days of initial receipt of the information.

(2) The establishment shall promptly investigate all adverse reactions that are subject of these 15-day reports and shall submit follow-up reports within 15 calendar days of the receipt of new information or as requested by FDA. If additional information is not obtainable, a follow-up report

may be required that describes briefly the steps taken to seek additional information and the reasons why it could not be obtained.

(3) Copies of the reporting form (FDA-3500A) may be obtained from the Center for Biologics Evaluation and Research (see address in paragraph (a)(4) of this section). Additional supplies of the form may be obtained from the Consolidated Forms and Publications Distribution Center, 3222 Hubbard Rd., Landover, MD 20785.

(4) The establishment shall submit two copies of each report described in this paragraph to the Center for Biologics Evaluation and Research (HFM-210), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448. FDA may waive the requirement for the second copy in appropriate circumstances.

(b) *Reports of product deviations.* (1) Any establishment that becomes aware of a product deviation in the manufacture of a distributed human cellular or tissue-based product shall immediately determine whether the product deviation is of the type that could reasonably be expected to lead to a reportable adverse reaction and, if it is, shall report the product deviation to the address in paragraph (b)(3) of this section as soon as possible.

(2) Each report shall contain a description of the product deviation and information on all corrective actions that have been or will be taken in response to the product deviation (e.g., recalls).

(3) Each report of a product deviation shall be reported to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research (HFM-600), 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448.

(c) *Records.* Reports and investigations required under this section shall be documented and records shall be maintained.

§ 1271.370 Labeling and claims.

(a) *Label information and accompanying materials.* (1) Each human cellular or tissue-based product made available for distribution shall be labeled clearly and accurately.

(2) The following information shall appear on the product label:

(i) Name and address of the establishment that determines that the product meets release criteria and makes the product available for distribution;

(ii) Description of the type of product; and

(iii) Expiration date, if any.

(3) The following information shall appear either on the product label or package insert:

(i) Storage temperature;

(ii) Warnings, where appropriate; and

(iii) Instructions for use.

(b) *Claims.* (1) All labeling, advertising, and promotional materials for a human cellular or tissue-based product shall be clear, truthful, and balanced in all respects, and may not be false or misleading in any particular.

(2) A labeling claim or promotional materials regarding the therapeutic or clinical outcome of a human cellular or tissue-based product (other than reconstruction, replacement, repair, or supplementation of cells or tissue) is considered a claim for a use other than a homologous use, as defined in § 1271.3(d), and the product, including labeling, shall be regulated under section 351 of the PHS Act and/or the Federal Food, Drug, and Cosmetic Act.

5. Subpart F, consisting of §§ 1271.390 through 1271.440, is added to part 1271 to read as follows:

Subpart F—Inspection and Enforcement of Establishments Described in § 1271.10

Sec.

Subpart F—Inspection and Enforcement of Establishments Described in § 1271.10

§ 1271.390 Applicability.

The provisions set forth in this subpart are applicable only to human cellular and tissue-based products described in § 1271.10 and regulated solely under section 361 of the Public Health Service Act (the PHS Act) and the regulations in this part, and to the establishments that manufacture those products. Human cellular and tissue-based products described in § 1271.15 and regulated as drugs, devices, and/or biological products under the act and/or section 351 of the PHS Act, and the establishments that manufacture those products, are not subject to the regulations set forth in this subpart.

§ 1271.400 Inspections.

(a) An establishment subject to this part as described in § 1271.10, including any location performing contract services, shall permit an authorized representative of the Food and Drug Administration (FDA) to make at any reasonable time and in a reasonable manner such inspection of the establishment, including but not limited to its facilities, equipment, processes, products, procedures, labeling, and records, as may be necessary in the judgment of such representative to determine compliance with the provisions of this part. Such inspection may be made with or without notice and will ordinarily be made during regular business hours.

(b) The frequency of inspection will be at the agency's discretion.

(c) FDA's representative will call upon the most responsible person available at the time of the inspection of the establishment and may question the personnel of the establishment as the representative deems necessary.

(d) FDA's representative may review and copy any records required to be kept under this part and may take photographs or make videotapes.

(e) The public disclosure of records containing the name or other positive identification of donors or recipients of human cellular or tissue-based products will be handled in accordance with FDA's procedures on disclosure of information as set forth in part 20 of this chapter.

§ 1271.420 Human cellular and tissue-based products offered for import.

(a) When a human cellular or tissue-based product is offered for entry, the importer of record shall notify the director of the district of the Food and Drug Administration (FDA) having jurisdiction over the port of entry through which the product is imported or offered for import, or such officer of the district as the director may designate to act in his or her behalf in administering and enforcing this part.

(b) A human cellular or tissue-based product offered for import shall be held intact, under conditions necessary to maintain product function and integrity and prevent transmission of communicable disease, until it is released by FDA.

§ 1271.440 Orders of retention, recall, destruction, and cessation of manufacturing.

(a) Upon an agency finding that a human cellular or tissue-based product or an establishment is in violation of the regulations in this part, an authorized Food and Drug Administration (FDA) representative may take one or more of the following actions:

(1) Serve upon the person who distributed the human cellular or tissue-based product a written order that the product be recalled and/or destroyed, as appropriate, and upon persons in possession of the product that the product shall be retained until it is recalled by the distributor, destroyed, or disposed of as agreed by FDA, or the safety of the product is confirmed;

(2) Take possession of and/or destroy the violative human cellular or tissue-based product; or

(3) Serve upon the establishment an order to cease manufacturing until compliance with the regulations of this part has been achieved.

(b) A written order issued under paragraph (a) of this section will state with particularity the facts that justify the order.

(c)(1) A written order issued under paragraph (a)(1) of this section will ordinarily provide that the human cellular or tissue-based product be recalled and/or destroyed within 5 working days from the date of receipt of the order. After receipt of an order issued under paragraph (a)(1) of this section, the establishment in possession of the human cellular or tissue-based product shall not distribute or dispose of the product in any manner except to recall and/or destroy the product consistent with the provisions of the order, under the supervision of an authorized FDA representative.

(2) In lieu of paragraph (c)(1) of this section, other arrangements for assuring the proper disposition of the human cellular or tissue-based product may be agreed upon by the person receiving the written order and an authorized official of FDA. Such arrangements may include, among others, providing FDA with records or other written information that adequately assure that the human cellular or tissue-based product has been recovered, processed, stored, and distributed in conformance with this part, and that, except as provided under §§ 1271.65 and 1271.90, the donor of the cells or tissue for the product has been determined to be suitable.

(d) A written order issued under paragraph (a)(3) of this section will specify the regulations with which compliance shall be achieved and will ordinarily specify the particular operations covered by the order. After receipt of an order issued under paragraph (a)(3) of this section, an establishment shall not resume operations without prior authorization of an authorized official of FDA.

(e) Within 5 working days of receipt of a written order for retention, recall, destruction, and/or cessation (or within 5 working days of the agency's possession of a human cellular or tissue-based product under paragraph (a)(2) of this section), the recipient of the written order or prior

possessor of such product may request a hearing on the matter in accordance with part 16 of this chapter. An order of destruction will be held in abeyance pending resolution of the hearing request.

Dated: AUG 29 2000

Jane E. Henney,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

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